

**1,2,4-TRIAZOLE DERIVATIVE, METHOD FOR PREPARING THE
SAME, AND PHARMACEUTICAL COMPOSITION CONTAINING THE
SAME**

BACKGROUND OF THE INVENTION

This U.S. non-provisional application claims priority under 35 U.S.C. §119 to Korean Patent Application No. 2002-46551, filed on August 7, 2002, in the Korean Intellectual Property Office, the contents of which are incorporated herein by reference in its entirety.

1. Field of the Invention

The present invention relates to a 1,2,4-triazole derivative or non-toxic salt thereof, a method for preparing the same, and a pharmaceutical composition containing the same as an active ingredient.

2. Description of the Related Art

Most nonsteroidal antiinflammatory agents are responsible for blocking the enzyme, cyclooxygenase (COX) or prostaglandin G/H synthase, thereby reducing inflammation, pain, or fever. In addition, they inhibit uterus contraction caused by hormones and also inhibit growth of several cancers. Cyclooxygenase-1 (COX-1) was first discovered in bovine. The COX-1 is constitutively expressed in a variety of cell types. Unlike the COX-1, cyclooxygenase-2 (COX-2) is a recently discovered isoform of cyclooxygenase that is easily inducible by mitogen, endotoxin, hormone, growth factor, or cytokine.

Prostaglandin is a potent mediator of various pathological and physiological processes. The COX-1 plays important physiological roles such as the release of endogenous prostaglandin, the maintenance of the shape, the function of stomach, and blood circulation in kidney. On the other hand, the COX-2 is induced by an inflammatory factor, hormone, growth factor, or cytokine. Therefore, the COX-2 is involved in pathological processes of prostaglandin unlike the constitutive COX-1.

In this regard, selective inhibitors of the COX-2 produce fewer and less side effects in terms of action mechanism in comparison with conventional nonsteroidal antiinflammatory agents. In addition, they reduce inflammation, pain, and fever and inhibit uterus contraction caused by hormones and growth of several cancers. In particular, they are effective in decreasing side effects such as stomach toxicity and

kidney toxicity. Still furthermore, they inhibit the synthesis of contractile prostanoid, thereby leading to suppression of the contraction of smooth muscles. Therefore, premature birth, menstrual irregularity, asthma, and eosinophilic disease can be prevented.

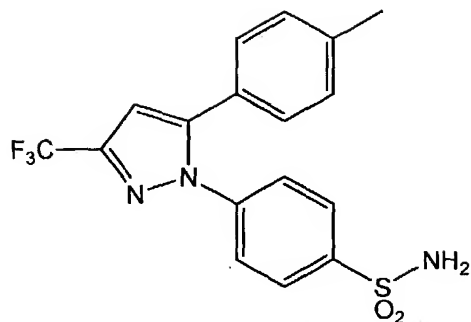
5 Recently, it was reported that nonsteroidal antiinflammatory agents are effective in treating large intestine cancer [*European Journal of Cancer*, Vol 37, p2302, 2001], prostate cancer [*Urology*, Vol 58, p127, 2001], and dementia [*Exp. Opin. Invest. Drugs*, Vol 9, p671, 2000].

10 In addition, it is anticipated that selective COX-2 inhibitors would be effective in treating osteoporosis and glaucoma. Utility of selective COX-2 inhibitors is well described in documents [John Vane, "Towards a Better Aspirin" in *Nature*, Vol.367, pp215-216, 1994; Bruno Battistini, Regina Botting and Y.S. Bakhle, "COX-1 and COX-2: Toward the Development of More Selective NSAIDs" in *Drug News and Perspectives*, 15 Vol.7, pp501-512, 1994; David B. Reitz and Karen Seibert, "Selective Cyclooxygenase Inhibitors" in *Annual Reports in Medicinal Chemistry*, James A. Bristol, Editor, Vol. 30, pp179-188, 1995].

Various selective COX-2 inhibitors having different structures have been known. Among them, a selective COX-2 inhibitor having a diaryl 20 heterocyclic structure, i.e. a tricyclic structure has been widely studied as a potent candidate. The diaryl heterocyclic structure has a central ring and a sulfonamide or methylsulfone group attached to one of the aryl rings. An initial substance having such diaryl heterocyclic structure is Dup697 [*Bioorganic & Medicinal Chemistry Letters*, Vol 5, p2123, 1995]. 25 Since then, SC-58635 having a pyrazol ring (*Journal of Medicinal Chemistry*, Vol 40, p1347, 1997) and MK-966 having a furanone ring (WO 95/00501) were discovered as derivatives of the Dup697.

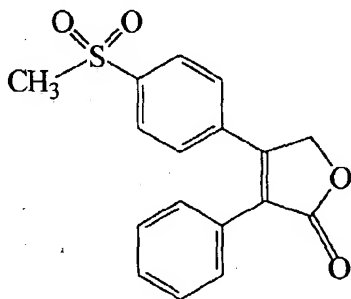
One selective COX-2 inhibitor, Celecoxib of formula 58 is disclosed in U.S. Patent No. 5,466,823. The Celecoxib is a substituted 30 pyrazolyl benzenesulfonamide derivative.

Formula 58



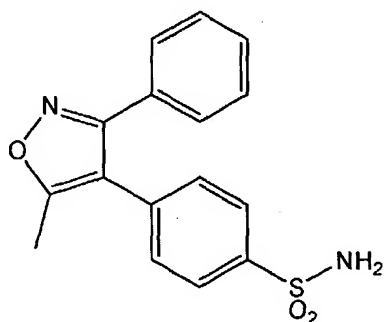
Another selective COX-2 inhibitor, Rofecoxib of formula 59 is disclosed in WO 95/00501. The Rofecoxib has a diaryl heterocyclic structure with a central furanone ring.

Formula 59



Valdecoxib of formula 60 as another selective COX-2 inhibitor is disclosed in U.S. Patent No. 5,633,272. The Valdecoxib has a phenylsulfonamide moiety with a central isoxazole ring.

Formula 60



The selective COX-2 inhibitors of formulas 58 to 60 are effective inflammatory therapeutic agents with fewer and less side effects in comparison with conventional nonsteroidal antiinflammatory agents.

SUMMARY OF THE INVENTION

An object of the present invention is to provide a 1,2,4-triazole derivative of formula 1 or a non-toxic salt thereof.

Another object of the present invention is to provide a method for preparing a 1,2,4-triazole derivative or a non-toxic salt thereof.

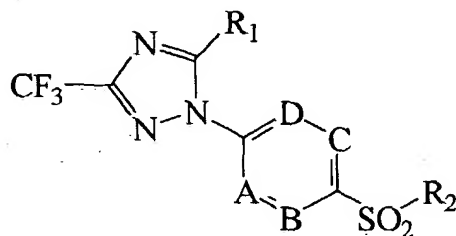
Another object of the present invention is to provide pharmaceutical compositions comprising a 1,2,4-triazole derivative or a non-toxic salt thereof as an active ingredient for the treatment of fever, pain, and inflammation.

Yet another object of the present invention is to provide a pharmaceutical composition comprising a 1,2,4-triazole derivative or a non-toxic salt thereof as an active ingredient for the treatment of cancers and dementia.

DETAILED DESCRIPTION OF THE INVENTION

According to an aspect of the present invention, there is provided 1,2,4-triazole derivatives represented by formula 1:

Formula 1



wherein:

R₁ is a C₃-C₆ cycloalkyl group; a C₃-C₆ cycloalkenyl group; a phenyl group; a phenyl group substituted with one or more selected from the group consisting of a C₁-C₆ alkyl group, a C₁-C₆ haloalkyl group, a C₁-C₆ alkoxy group, a C₁-C₆ haloalkoxy group, a halogen group, an amino group, a monoalkylamino group, a dialkylamino group, a nitro group, and a cyano group; a styrenyl group; a C₁-C₆ alkoxy styrenyl group; or a pyridyl group;

R₂ is a methyl or amino group; and

A, B, C, and D are independently carbon or nitrogen;
or a non-toxic salt thereof.

The 1,2,4-triazole derivative of formula 1 may be present in the form of a non-toxic salt. The term, "non-toxic salt" as used herein refers to a pharmaceutically acceptable, toxin-free salt, including an organic salt and an inorganic salt.

The Inorganic salt of the 1,2,4-triazole derivative of formula 1 includes an inorganic salt of aluminum, ammonium, calcium, copper, iron,

lithium, magnesium, manganese, potassium, sodium, or zinc but is not limited thereto. An inorganic salt of ammonium, calcium, potassium, or sodium is preferable.

The organic salt of the 1,2,4-triazole derivative of formula 1 includes an organic amine salt of primary, secondary, or tertiary amine, substituted amine that is present in nature, or cyclic amine, or a salt of a basic ion exchange resin but is not limited thereto. Examples of the salt of a basic ion exchange resin include, but are not limited to, a salt of arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, N-methylglucamine, glucamine, glucosamine, histidine, N-(2-hydroxyethyl)piperidine, N-(2-hydroxyethyl)pyrrolidine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resin, procaine, purine, triethylamine, trimethylamine, and tripropylamine.

The 1,2,4-triazole derivative of formula 1 may be present in the form of an organic acid salt or an inorganic acid salt.

Examples of the organic acid salt or the inorganic acid salt of the 1,2,4-triazole derivative of formula 1 include, but are not limited to, a salt of acetic acid, adipic acid, aspartic acid, 1,5-naphthalene disulfonic acid, benzene sulfonic acid, benzoic acid, camphor sulfonic acid, citric acid, 1,2-ethane disulfonic acid, ethane sulfonic acid, ethylenediaminetetraacetic acid, fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, hydroiodic acid, hydrobromic acid, hydrochloric acid, isethionic acid, lactic acid, maleic acid, malic acid, mandelic acid, methane sulfonic acid, mucic acid, 2-naphthalenedisulfonic acid, nitric acid, oxalic acid, pentothenic acid, phosphoric acid, pivalic acid, propionic acid, salicylic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, p-toluene sulfonic acid, undecanoic acid, and 10-undecenoic acid. A salt of succinic acid, hydrobromic acid, hydrochloric acid, maleic acid, methanesulfonic acid, phosphoric acid, sulfuric acid, or tartaric acid is preferable.

A preferred group of the 1,2,4-triazole derivative of the present invention is as follows:

1-(4-methanesulfonylphenyl)-5-phenyl-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(4-bromophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3-bromophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5 5-(4-fluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,5-dichloro-4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(4-chlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

10 5-(3,4-dichlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,4-dimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

15 5-(3,4-difluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

1-(4-methanesulfonylphenyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,4-dimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

20 1-(4-methanesulfonylphenyl)-5-p-tolyl-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,4-dimethylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

25 5-(3-chloro-4-methylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(4-chloro-3-methylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3-chloro-4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

30 5-(4-chloro-3-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3-fluoro-4-methylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

35 5-(4-fluoro-3-methylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3-fluoro-4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

- 1-(4-methanesulfonylphenyl)-3-trifluoromethyl-5-(4-trifluoromethylphenyl)-1H-[1,2,4]triazole;
- 5-(4-ethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5 1-(4-methanesulfonylphenyl)-5-(4-trifluoromethoxyphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(4-t-butylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(4-cyanophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 10 5-[4-(N-methylamino)-phenyl]-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-[4-(N,N-dimethylamino)-phenyl]-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 15 5-(4-aminophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(3-trifluoromethylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(3-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 20 1-(4-methanesulfonylphenyl)-5-m-tolyl-3-trifluoromethyl-1H-[1,2,4]triazole;
- 1-(4-methanesulfonylphenyl)-5-o-tolyl-3-trifluoromethyl-1H-[1,2,4]triazole;
- 25 5-(2-bromophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(2-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(2,4-difluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 30 5-(2,5-difluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(2,4,5-trifluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 35 5-(2,3-dichlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;
- 5-(2,4-dichlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,5-difluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,5-dimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5 5-(2,4-dimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(3,4,5-trimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

10 5-(2-fluoro-4-trifluoromethylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(2-chloro-4-nitrophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-(2,4-dichloro-5-fluorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

15 5-(3-fluoro-4-methylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-benzo[1,3]dioxol-5-yl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine;

20 5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-ethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine;

25 5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-t-butylphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-cyanophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-aminophenyl)-[1,2,4]triazol-1-yl]pyridine;

30 5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-N-methylaminophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(4-N,N-dimethylaminophenyl)-[1,2,4]triazol-1-yl]pyridine;

35 5-methanesulfonyl-2-[3-trifluoromethyl-5-(3-methylphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3-methoxyphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,4-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,5-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,4,5-trifluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,3-dichlorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,4-dichlorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3,5-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3,5-dimethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,4-dimethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3,4,5-trifluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2-fluoro-4-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2-chloro-4-nitrophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(2,4-dichloro-5-fluorophenyl)-[1,2,4]triazol-1-yl]pyridine;

5-methanesulfonyl-2-[3-trifluoromethyl-5-(3-fluoro-4-methylphenyl)-[1,2,4]triazol-1-yl]pyridine;

2-(5-benzo[1,3]dioxol-5-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-5-methanesulfonyl pyridine;

3-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl]pyridine;

4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl]pyridine;

5-cyclohexyl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

5-cyclohexen-1-yl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole;

4-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;
 e;
 4-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 5 4-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 10 4-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 15 4-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;
 e;
 4-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 20 4-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 25 4-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 30 4-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 35 4-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide;
 4-[3-trifluoromethyl-5-(4-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(4-ethoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

5 4-[3-trifluoromethyl-5-(4-*t*-butylphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(4-cyanophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(4-aminophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

10 4-[3-trifluoromethyl-5-(4-*N*-methylaminophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(4-*N,N*-dimethylaminophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

15 4-[3-trifluoromethyl-5-*m*-tolyl-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(3-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(3-methoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

20 4-[3-trifluoromethyl-5-(2-bromophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2-methoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

25 4-[3-trifluoromethyl-5-(2,4-difluorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2,5-difluorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2,4,5-trifluorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

30 4-[3-trifluoromethyl-5-(2,3-dichlorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2,4-dichlorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

35 4-[3-trifluoromethyl-5-(3,5-dimethoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2,4-dimethoxyphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(3,4,5-trifluorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2-fluoro-4-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

5 4-[3-trifluoromethyl-5-(2-chloro-4-nitrophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-[3-trifluoromethyl-5-(2,4-dichloro-5-fluorophenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

10 4-[3-trifluoromethyl-5-(3-fluoro-4-methylphenyl)-[1,2,4]triazol-1-yl]benzenesulfonamide;

4-(5-benzo[1,3]dioxol-5-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;

4-(5-pyridine-3-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;

15 4-(5-pyridin-4-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;

4-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;

20 4-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamide;

5-methanesulfonyl-2-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine;

2-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

25 2-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

2-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

30 2-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

2-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

5-methanesulfonyl-2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine;

35 2-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

5-methanesulfonyl-2-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine;

- 2-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;
- 2-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;
- 5 2-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;
- 6-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 10 6-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(4-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 15 6-[3-trifluoromethyl-5-(4-ethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(4-trifluoromethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(4-*t*-butylphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 20 6-[3-trifluoromethyl-5-(4-cynophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(4-aminophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 25 6-[3-trifluoromethyl-5-(4-*N*-methylaminophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(4-*N,N*-dimethylaminophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-*m*-tolyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 30 6-[3-trifluoromethyl-5-(3-methoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(3-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 35 6-[3-trifluoromethyl-5-(2-bromophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[3-trifluoromethyl-5-(2-methoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(2,4-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(2,5-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

5 6-[3-trifluoromethyl-5-(3,5-difluorophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(2,4,5-trifluorophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(2-fluoro-4-trifluoromethylphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

10 6-[3-trifluoromethyl-5-(2,4-dimethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(3,4,5-trimethoxyphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

15 6-[3-trifluoromethyl-5-(2-chloro-4-nitrophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(2,4-difluoro-5-fluorophenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

6-[3-trifluoromethyl-5-(3-fluoro-4-methylphenyl)-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

20 2-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

2-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

25 2-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine;

5-methanesulfonyl-2-((3-pyridinyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl))pyridine;

5-methanesulfonyl-2-((4-pyridinyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl))pyridine;

30 2-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-5-methanesulfonyl pyridine;

2-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-5-methanesulfonyl pyridine;

35 6-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;

6-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;

- 6-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 5 6-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 10 6-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;
- 15 6-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 20 6-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 25 6-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 30 6-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-3-sulfonic acid amide;
- 6-(5-pyridin-3-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;
- 35 6-(5-pyridin-4-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;
- 6-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;

6-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-3-sulfonic acid amide;

2-methanesulfonyl-5-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine;

5 5-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

10 5-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

15 2-methanesulfonyl-5-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine;

5-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

20 2-methanesulfonyl-5-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine;

5-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

25 5-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-pyridine-2-sulfonic acid amide;

30 5-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

35 5-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-2-methanesulfonyl pyridine;

5-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-2-methanesulfonyl pyridine;

5-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-2-methanesulfonyl pyridine;

5 5-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

5-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

10 5-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

15 5-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

20 5-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

5-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

25 5-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

30 5-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

35 5-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine-2-sulfonic acid amide;

5-(5-pyridin-3-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

5 5-(5-pyridin-4-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

5-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

5-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridine-2-sulfonic acid amide;

10 3-methanesulfonyl-6-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine;

3-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

15 3-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

20 3-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-methanesulfonyl-6-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine;

25 3-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-methanesulfonyl-6-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine;

3-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

30 3-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

35 3-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine;

3-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-
6-methanesulfonyl pyridazine;

3-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-
6-methanesulfonyl pyridazine;

5 3-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-
6-methanesulfonyl pyridazine;

3-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-
-1-yl]-6-methanesulfonyl pyridazine;

3-methanesulfonyl-6-(5-pyridin-3-yl-3-trifluoromethyl-[1,2,4]triazol-
10 1-yl)pyridazine;

3-methanesulfonyl-6-(5-pyridin-4-yl-3-trifluoromethyl-[1,2,4]triazol-
1-yl)pyridazine;

3-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-6-methanesulf
onyl pyridazine;

15 3-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)-6-methan
esulfonyl pyridazine;

6-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfoni
c acid amide;

6-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine
20 -3-sulfonic acid amide;

6-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-
3-sulfonic acid amide;

6-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridaz
ine-3-sulfonic acid amide;

25 6-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine
-3-sulfonic acid amide;

6-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrida
zine-3-sulfonic acid amide;

6-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazi
30 ne-3-sulfonic acid amide;

6-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyri
dazine-3-sulfonic acid amide;

6-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfoni
c acid amide;

35 6-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrida
zine-3-sulfonic acid amide;

6-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]
pyridazine-3-sulfonic acid amide;

6-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

6-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

5 6-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

6-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

6-[5-(4-fluoro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

10 6-[5-(3-fluoro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

6-[5-(3,5-dichloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridazine-3-sulfonic acid amide;

15 6-(5-pyridin-3-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfonic acid amide;

6-(5-pyridin-4-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfonic acid amide;

6-(5-cyclohexyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfonic acid amide;

20 6-(5-cyclohexen-1-yl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyridazine-3-sulfonic acid amide;

5-methanesulfonyl-2-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyrimidine;

25 2-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

30 2-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

35 5-methanesulfonyl-2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine;

2-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

5-methanesulfonyl-2-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyrimidine;

2-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

5 2-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

10 2-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

2-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyrimidine;

15 2-(5-phenyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyrimidine-5-sulfonic acid amide;

2-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(4-fluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

20 2-[5-(3,4-difluorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(4-chlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

25 2-[5-(3,4-dichlorophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(3,4-dimethoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

30 2-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)pyrimidine-5-sulfonic acid amide;

2-[5-(3,4-dimethylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

35 2-[5-(3-chloro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(4-chloro-3-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(3-chloro-4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

2-[5-(4-chloro-3-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

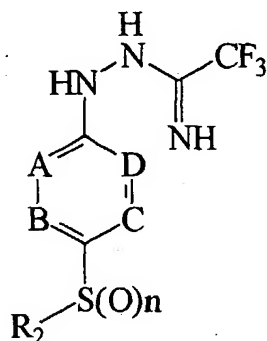
5 2-[5-(3-fluoro-4-methylphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyrimidine-5-sulfonic acid amide;

5-styryl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole; or

10 5-[2-(4-methoxyphenyl)-vinyl]-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole.

According to another aspect of the present invention, there is provided an amidrazone derivative as an intermediate for the synthesis of the 1,2,4-triazole derivative of formula 1, as represented by formula 4:

Formula 4



15

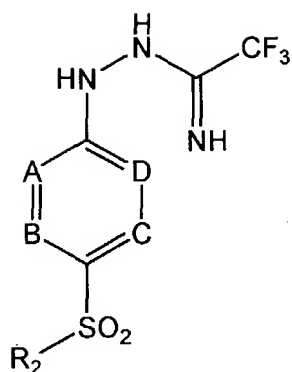
wherein, R₂, A, B, C, and D are as defined in formula 1 and n is an integer of 0 to 2.

According to another aspect of the present invention, there is provided a method for preparing a 1,2,4-triazole derivative of formula 1 or a non-toxic salt thereof, comprising reacting an amidrazone derivative of formula 4a with acyl chloride of formula 5 in the presence of base.

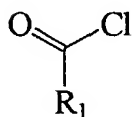
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25

Formula 4a



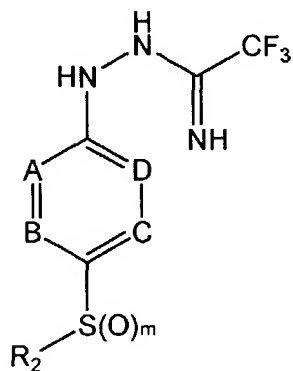
Formula 5



wherein, R_1 , R_2 , A, B, C, and D are as defined in formula 1.

5 According to another aspect of the present invention, there is provided a method for preparing a 1,2,4-triazole derivative of formula 1 or a non-toxic salt thereof, comprising reacting an amidrazone derivative of formula 4b with acyl chloride of formula 5 in the presence of base and oxidizing the resultant compound with an oxidizing agent selected from
10 the group consisting of magnesium monoperoxyphthalate hexahydrate (MMPP), m-chloroperoxybenzoic acid (MCPBA), and potassium peroxymonosulfate.

Formula 4b



15 wherein, R_2 , A, B, C, and D is as defined in formula 1 and m is 0 or 1.

The above mentioned reactions are preferably carried out in a polar solvent. Examples of the polar solvent include, but are not limited to, dimethylformamide, 1,4-dioxane, dimethylsulfoxide,
20 N-methylpyrrolidinone, or m-xylene.

The reactions are preferably carried out at a temperature of -10 to 110°C. A reaction time is determined depending on reactants. Generally, a reaction time of 10 minutes to 36 hours is required.

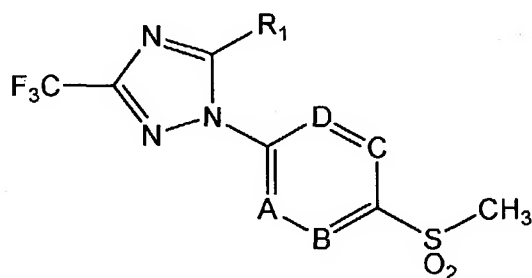
When the reactions are completed, the reaction resultants are
5 extracted with water and an organic solvent such as ethyl acetate, dichloromethane, tetrahydrofuran, and ether, to remove salts. The crude extracts are purified by silica gel column chromatography to give the final products.

Bases to be used herein are organic bases or inorganic bases.
10 The preferred organic bases are triethyl amine, trimethyl amine, tripropyl amine, pyridine, or imidazole. The preferred inorganic bases are sodium acetate, sodium hydroxide, sodium hydride, potassium hydroxide, sodium carbonate, or potassium carbonate. Pyridine is the most preferred.

15 The oxidative reaction is preferably carried out in dichloromethane in the presence of an oxidizing agent. The preferred oxidizing agent is MMPP, MCPBA, or potassium peroxymonosulfate.

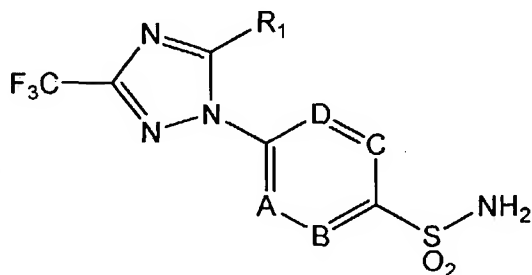
According to another aspect of the present invention, there is provided a method for preparing a compound of formula 1b, comprising
20 reacting a compound of formula 1a with hydroxylamine or a salt thereof in the presence of a strong base and a Lewis acid.

Formula 1a



25

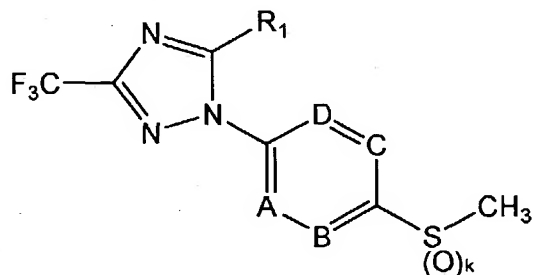
Formula 1b



wherein, R_1 , A, B, C, and D are as defined in formula 1.

According to another aspect of the present invention, there is provided a method for preparing a 1,2,4-triazole derivative of formula 1b or a non-toxic salt thereof, comprising reacting a compound of formula 6a with hydroxylamine or a salt thereof in the presence of a strong base and a Lewis acid and oxidizing the resultant compound using an oxidizing agent selected from the group consisting of MMPP, MCPBA, and potassium peroxymonosulfate.

Formula 6a



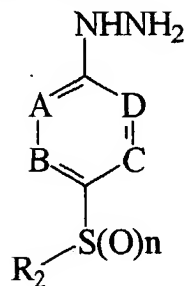
wherein, R_1 , A, B, C, and D are as defined in formula 1 and k is 1 or 0.

The preferred hydroxylamine salt is hydroxylamine sulfate, hydroxylamine hydrochloride, hydroxylamine phosphate, hydroxylamine nitrate, or hydroxylamine sulfonate.

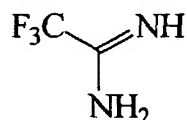
In order to prepare a compound in which R_2 is a amino group in formula 1, at first, a compound of formula 1a or a compound of formula 6a is dehydrogenated in a solvent of tetrahydrofuran or ether at -78 to $80^\circ C$ in the presence of a strong base of alkyl lithium, aryl lithium, alkyl magnesium chloride, or aryl magnesium chloride. Then, the resultant compound is reacted with a Lewis acid such as alkylboron, arylboron, alkylaluminium, and arylaluminium at -78 to $80^\circ C$, followed by amination using hydroxylamine sulfate. Preferably, hydroxylamine sulfate is used because when excess hydroxylamine sulfate is used, side reactions are minimal and the residual hydroxylamine sulfate and byproducts are easily removed upon extraction. After extraction, a crude extract is purified by column chromatography to produce a product having a desired sulfonamide group.

According to another aspect of the present invention, there is provided a method for preparing a compound of formula 4, comprising reacting a hydrazine derivative of formula 2 with trifluoroacetimidine of formula 3 in the presence of base.

Formula 2



Formula 3



5 wherein, R_2 , A, B, C, D, and n are as defined in formula 4.

The reaction is carried out in a solvent. The preferred solvent is methanol or a mixed solvent of methanol and tetrahydrofuran. The reaction is preferably carried out at a temperature of -10 to 66°C . A reaction time is determined depending on reactants. Preferably, the
10 reaction time is 10 minutes to 48 hours.

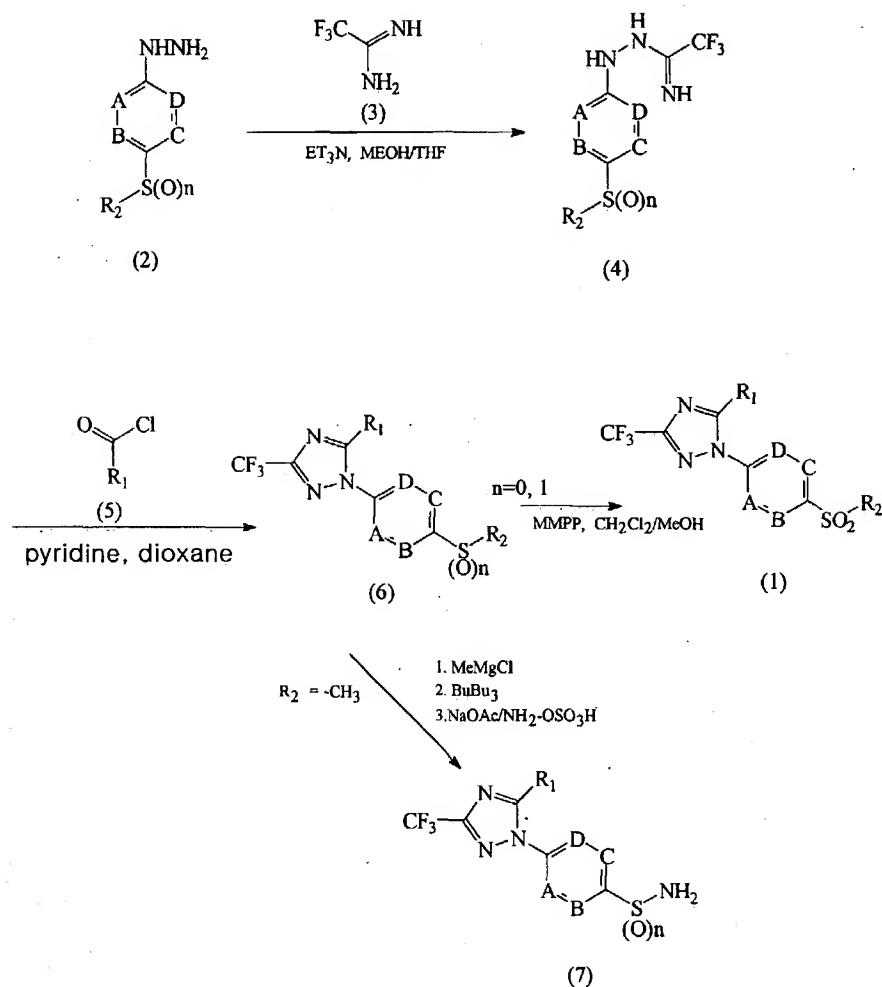
When the reaction is completed, the reaction resultant is extracted with water and an organic solvent such as ethyl acetate, dichloromethane, tetrahydrofuran, and ether, to remove salts. The crude extract is purified by silica gel column chromatography to give the
15 compound of formula 4.

The base to be used herein is an organic base or an inorganic base. Preferably, the organic base is triethyl amine, trimethyl amine, tripropyl amine, pyridine, or imidazole. Preferably, the inorganic base is sodium acetate, sodium hydroxide, sodium hydride, potassium hydroxide,
20 sodium carbonate, or potassium carbonate. More preferably, triethylamine is used.

All crude products obtained from the above mentioned reactions are purified via a conventional post-treatment process, for example, chromatography and recrystallization to thereby give final products.

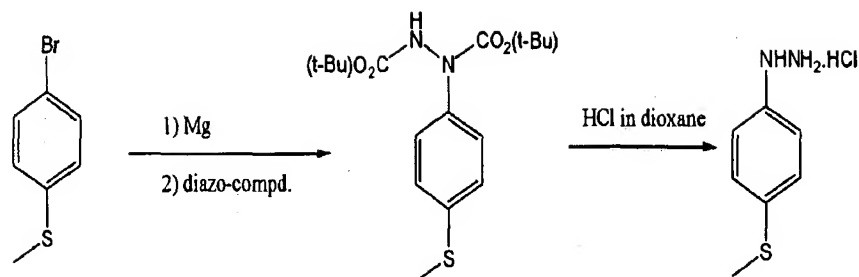
25 A method for preparing a compound of formula 1 is expressed by the following scheme 1:

Scheme 1



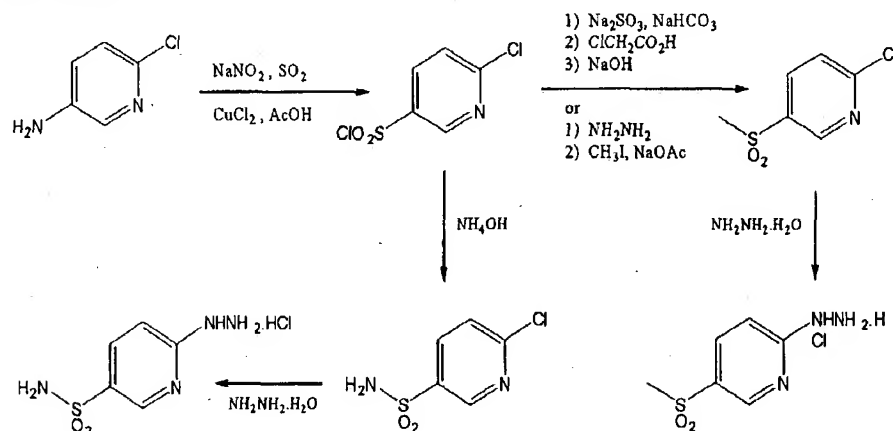
As a hydrazine derivative to be used in the scheme 1, 4-hydrazinobenzenesulfonamide hydrochloride can be obtained from Maybridge (United Kingdom). Other hydrazine derivatives can be synthesized as it is or in the form of their hydrochlorides according to known methods [*Tetrahedron Letters*, vol 28, No 42, p4933, 1987; U.S. Patent No. 4,204,870; *The Journal of Organic Chemistry*, vol 56, No 16, p4974, 1991; EP 1104759; and *Tetrahedron*, vol 48, No 21, p6791, 1989]. The synthesis methods of representative hydrazine derivatives are presented in Schemes 2 to 5.

Scheme 2



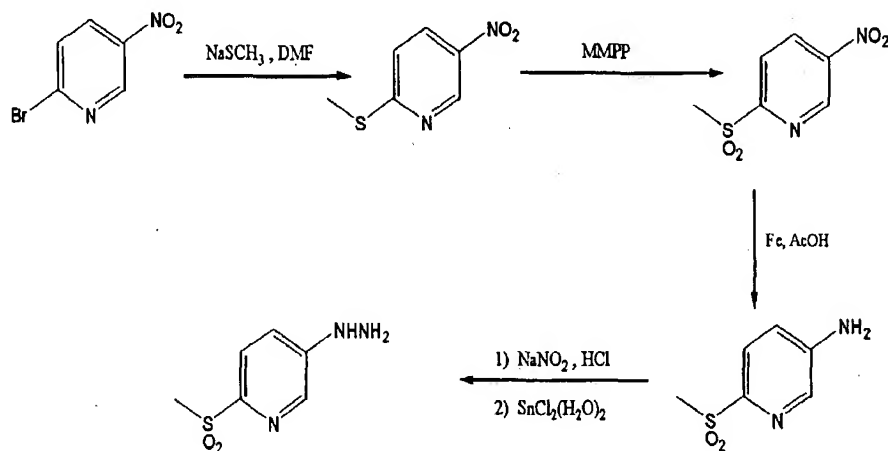
In Scheme 2, 4-bromo thioanisole is treated with magnesium to produce a Grignard compound. The Grignard compound reacts with a diazo compound and then hydrogen chloride to thereby produce a hydrochloride salt of hydrazine derivative.

Scheme 3



In Scheme 3, a pyridine derivative reacts with hydrazine monohydrate to produce a 2-hydrazinopyridine derivative.

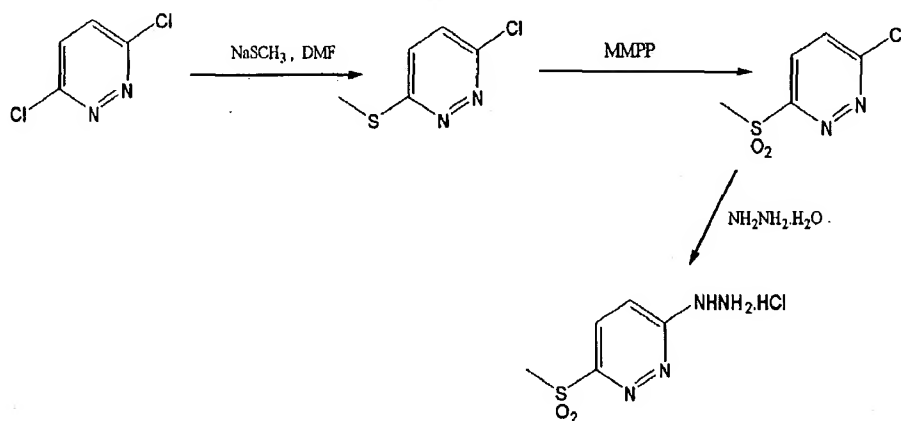
Scheme 4



In Scheme 4, a nitro-substituted pyridine derivative is reduced to an amine-substituted pyridine derivative. Then, a hydrazine group is introduced to the amine-substituted pyridine derivative to produce a 3-hydrazinopyridine derivative.

5

Scheme 5



In Scheme 5, a 2-hydrazinopyridazine derivative is prepared from 2,5-dichloro pyridazine according to a similar method as in the scheme 3.

In methods for preparing compounds of the present invention, reaction conditions such as types and amounts of solvent, base, and reactants are not limited to those as mentioned in the above. It is understood that a person of ordinary skill in the art can easily prepare compounds of the present invention through any combination of synthesis methods as described in the specification or as disclosed in known documents.

10

15

According to another aspect of the present invention, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a 1,2,4-triazol derivative or a non-toxic salt thereof as an active ingredient and a pharmaceutically acceptable carrier for the treatment of fever, pain, and inflammation.

20

The pharmaceutical composition comprises a compound of formula 1 or a non-toxic salt thereof when it is a selective inhibitor of cyclooxygenase-2. Therefore, the pharmaceutical composition can be used as an antipyretic, an analgesic, and an antiinflammatory agent, with minimal side effects.

25

Conventional nonsteroidal antiinflammatory agents non-selectively inhibit the prostaglandin synthesis enzymes, cyclooxygenase-1 and cyclooxygenase-2. Therefore, various side effects may occur.

On the other hand, a compound of formula 1 and a non-toxic salt thereof selectively inhibit cyclooxygenase-2. Therefore, the side effects of conventional nonsteroidal antipyretics, analgesics, and antiinflammatory agents can be reduced.

5 The pharmaceutical composition of the present invention comprises a compound of formula 1 and/or a non-toxic salt thereof and a pharmaceutically acceptable carrier or excipient. Therefore, the pharmaceutical composition may be used as a substitute for conventional nonsteroidal antiinflammatory agents. In particular, due to
10 the reduction of the side effects of conventional nonsteroidal antipyretics, analgesics, and antiinflammatory agents, the pharmaceutical composition of the present invention is useful for treating patients with peptic ulcer, gastritis, regional enteritis, ulcerative colitis, diverticulitis, gastrorrhagia, or hypoprothrombinemia.

15 The pharmaceutical composition of the present invention can be used in all inflammatory diseases associated with pathological prostaglandin and is particularly appropriate for treating osteoarthritis and rheumatoid arthritis which require high dosage of nonsteroidal antiinflammatory agents.

20 The pharmaceutical composition of the present invention can be administered in the form of an adult dosage of 1 mg/day to 1000 mg/day of the compound of formula 1. An adequate dosage is determined depending on the degree of disease severity.

 According to yet another aspect of the present invention, there is
25 provided a pharmaceutical composition comprising a therapeutically effective amount of a 1,2,4-triazole derivative of formula 1 or a non-toxic salt thereof and a pharmaceutically acceptable carrier for the treatment of cancers and dementia.

 Recently, it was reported that nonsteroidal antiinflammatory
30 agents are effective for the treatment of large intestine cancer [*European Journal of Cancer*, Vol 37, p2302, 2001], prostate cancer [*Urology*, Vol 58, p127, 2001], and dementia [*Exp. Opin. Invest. Drugs*, Vol 9, p671, 2000]. Therefore, it is understood that the pharmaceutical composition of the present invention as a nonsteroidal antiinflammatory agent can
35 also be used for the treatment of these diseases.

 The pharmaceutical composition of the present invention can be administered in the form of an adult dosage of 1 mg/day to 1000 mg/day

of the compound of formula 1 or a non-toxic salt thereof. An adequate dosage is determined depending on the degree of disease severity.

The pharmaceutical composition of the present invention may be administered in the form of tablet, foam tablet, capsule, granule, powder, 5 sustained-release tablet, sustained-release capsule (a single unit formulation or a multiple unit formulation), intravenous and intramuscular injectable solution, infusion solution, suspension, or suppository, or in other suitable dosage forms.

Sustained-release pharmaceutical dosage forms contain active 10 ingredients with or without an initial loading dose. They are wholly or partially sustained-release pharmaceutical dosage forms to release active ingredients in a controlled manner.

Preferably, the pharmaceutical composition is orally administered.

The pharmaceutical composition further comprises a 15 pharmaceutically acceptable excipient and/or diluent and/or adjuvant in pharmaceutically effective amounts.

Examples of the excipient and adjuvant include gellatin, a natural sugar such as sucrose and lactose, lecitin, pectin, starch such as corn starch and amylose, cyclodextrin and cyclodextrin derivative, dextran, 20 polyvinylpyrrolidone, polyvinyl acetate, Arabic gum, arginic acid, xylose, talc, salicylic acid, calcium hydrogen phosphate, cellulose, cellulose derivative such as methylcellulose, methoxypropyl cellulose, hydroxypropylmethyl cellulose, and hydroxypropylmethylcellulose phthalate, fatty acid having 12 to 22 carbon atoms, emulsifying agent, oil 25 and fat, in particular, vegetable glycerol ester and polyglycerol ester of saturated fatty acids, monohydric alcohol, polyhydric alcohol, polyglycol such as polyethylene glycol, aliphatic alcohol having 1 to 20 carbon atoms, or aliphatic saturated or unsaturated fatty acid ester having 2 to 22 carbon atoms with polyhydric alcohols such as glycol, glycerol, 30 diethylene glycol, 1,2-propylene glycol, sorbitol, and mannitol.

Other suitable adjuvants include a disintegrating agent. Examples of the disintegrating agent include a cross-linked polyvinylpyrrolidone, sodium carboxymethyl starch, sodium carboxymethyl cellulose, and microcrystalline cellulose. A coating agent 35 which is conventionally used in this field may also be used. Examples of the coating agent include acrylic acid and/or methacrylic acid and/or an ester polymer or copolymer thereof, zein, ethyl cellulose, ethyl cellulose succinate, and Shellac.

Plasticizers suitable for the coating agent are citric ester and tartaric ester, glycerol and glycerol ester, or polyethylene glycol with different chain lengths.

5 A liquid composition such as solution and suspension is formulated in water or a physiological acceptable organic solvent such as alcohol and aliphatic alcohol.

The liquid pharmaceutical composition may further comprise a preservative such as potassium solvate, methyl 4-hydroxybenzoate, and propyl 4-hydroxybenzoate, an antioxidant such as ascorbic acid, and a
10 fragrant such as peppermint oil.

In addition, when the liquid pharmaceutical composition is formulated, a conventional solubilizer or emulsifier such as polyvinylpyrrolidone and polysolvate 80 may be used.

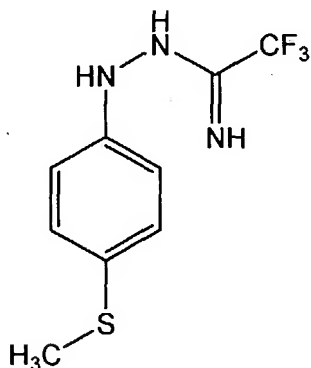
Other examples of suitable excipients and adjuvants are disclosed
15 in Dr.H.P. Fielder, "Lexikon der Hilfsstoffe fur Pharmazie, Kosmetik und angrenzende Gebiete" [Encyclopaedia of auxiliaries for pharmacy, cosmetics and related fields].

Hereinafter, the present invention will be described more specifically by examples. However, the following examples are provided
20 only for illustrations and thus the present invention is not limited to or by them.

Example 1

N-(4-methylsulfanylphenyl)trifluoroacetamidrazone

25 Formula 8



1.0 g (5.24 mmol) of 4-methylsulfanylphenylhydrazine hydrochloride was dissolved in 40 ml of a 1:1 mixed solvent of methanol and tetrahydrofuran and 0.80 ml (5.76 mmol) of triethylamine was added

dropwise. The reaction mixture was stirred at room temperature for 30 minutes and 0.90 g (6.81 mmol) of 85% trifluoro acetimidine was added dropwise. The reaction mixture was stirred at room temperature for 24 hours. When the reaction was completed, water and ethyl acetate were added to the reaction mixture. The water layer was twice extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 2/8) to give 0.88 g of the title compound as a liquid (yield 67%).

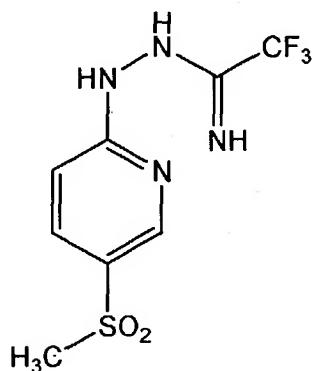
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ 2.55 (s, 3H), 5.45 (s, 2H, br), 7.40 (d, 2H, $J = 8.0$ Hz), 7.60 (d, 2H, $J = 8.0$ Hz), 9.70 (s, 1H).

15

Example 2

N-(5-methanesulfonylpyridin-2-yl)trifluoroacetamidrazone

Formula 9



205 mg (yield 54%) of the title compound as a solid was prepared in the same manner as in Example 1 except using 300 mg (1.34 mmol) of 5-methanesulfonylpyridin-2-yl hydrazine hydrochloride instead of 4-methylsulfonylphenylhydrazine hydrochloride.

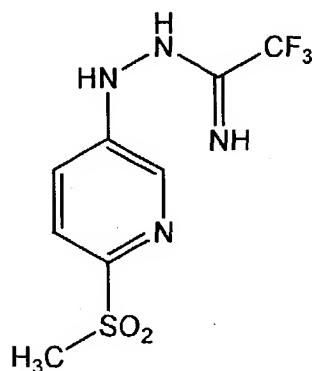
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ 2.90 (s, 3H), 5.65 (s, 2H, br), 6.95 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 2.8$ Hz), 7.80 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 2.0$ Hz), 9.70 (d, 1H, $J = 2.8$ Hz), 9.75 (s, 1H).

5

Example 3

N-(2-methanesulfonylpyridin-5-yl)trifluoroacetamidrazone

Formula 10



10

194 mg (yield 51%) of the title compound as a solid was prepared in the same manner as in Example 1 except using 300 mg (1.34 mmol) of 2-methanesulfonylpyridin-5-yl hydrazine hydrochloride instead of 4-methylsulfonylphenylhydrazine hydrochloride.

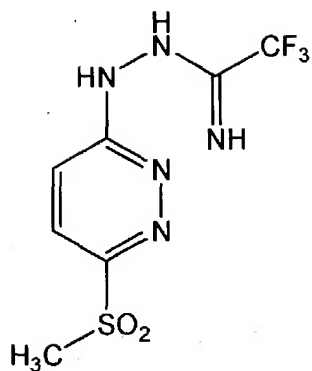
15 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 3.35 (s, 3H), 5.65 (s, 2H, br), 6.95 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 2.8$ Hz), 7.80 (dd, 1H, $J_1 = 9.0$ Hz, $J_2 = 2.0$ Hz), 9.70 (d, 1H, $J = 2.8$ Hz), 9.75 (s, 1H).

Example 4

N-(6-methanesulfonylpyridazin-3-yl)trifluoroacetamidrazone

Formula 11

20

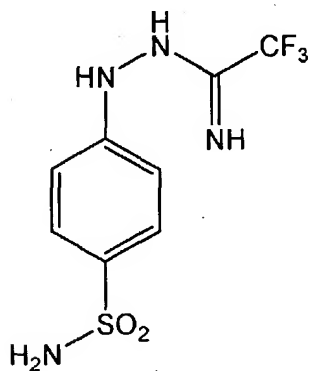


0.8 g (yield 64%) of the title compound as a solid was prepared in the same manner as in Example 1 except using 1.0 g (4.45 mmol) of 6-methanesulfonylpyridazin-3-yl hydrazine hydrochloride instead of 4-methylsulfanylphenylhydrazine hydrochloride.

¹H-NMR (400MHz, CDCl₃): δ 3.45 (s, 3H), 7.15 (s, 2H, br), 7.45 (d, 1H, J = 9.5 Hz), 8.00 (d, 1H, J = 9.5 Hz), 10.80 (s, 1H).

Example 5

N-(4-sulfonamidophenyl)trifluoroacetamidrazone
Formula 12



0.9 g (yield 68%) of the title compound as a solid was prepared in the same manner as in Example 1 except using 1.0 g (4.47 mmol) of 4-hydrazinobenzenesulfonamide hydrochloride instead of 4-methylsulfanylphenylhydrazine hydrochloride.

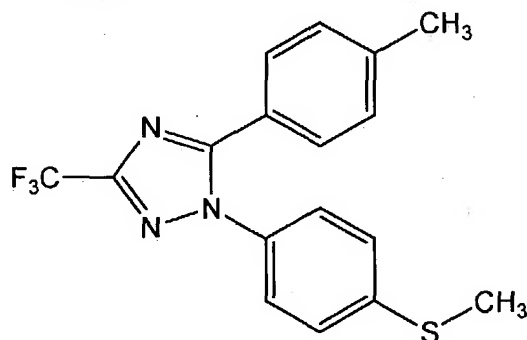
¹H-NMR (400MHz, CDCl₃): δ 5.45 (s, 2H, br), 7.31 (s, 2H), 7.40 (d, 2H, J = 8.0 Hz), 7.60 (d, 2H, J = 8.0 Hz), 9.70 (s, 1H).

5

Example 6

10 1-(4-methylsulfanylphenyl)-5-p-tolyl-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 13



220 mg (0.88 mmol) of
15 N-(4-methylsulfanylphenyl)trifluoroacetamidrazone was dissolved in 5 ml
of 1,4-dioxane and 0.08 ml (0.97 mmol) of pyridine was added dropwise.
The reaction mixture was stirred at room temperature for 10 minutes
and 150 mg (0.97 mmol) of p-toluoyl chloride was added dropwise. The
reaction mixture was stirred at the boiling point under reflux for 24 hours.
20 When the reaction was completed, the reaction mixture was cooled to
room temperature and water and ethyl acetate were added thereto.
The water layer was twice extracted with ethyl acetate. The combined
organic layer was once washed with saturated sodium chloride solution
and dried over anhydrous magnesium sulfate, and filtered under reduced
25 pressure. The obtained crude product was purified by flash column
chromatography (ethyl acetate/n-hexane = 2:8) to give 210 mg of the title
compound as an oil (yield 65%).

¹H-NMR (400MHz, CDCl₃): δ 2.35 (s, 3H); 2.55 (s, 3H), 7.15 (d,
2H, J = 8.0 Hz), 7.20-7.30 (m, 4H), 7.45 (d, 2H, J = 8.0 Hz).

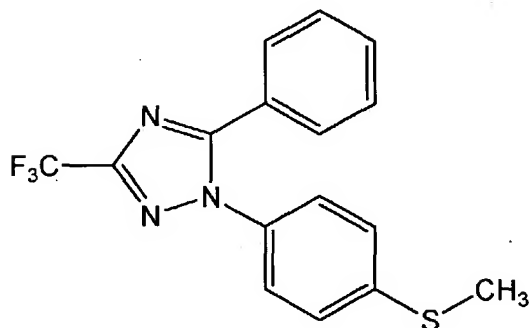
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Example 7

1-(4-methylsulfanylphenyl)-5-phenyl-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 14



10

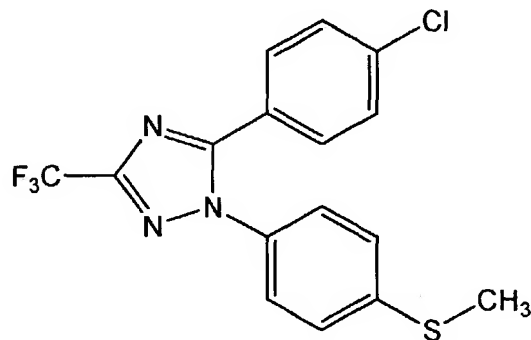
210 mg (yield 71%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 140 mg (0.97 mmol) of benzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification.

15

Example 8

5-(4-chlorophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 15



20

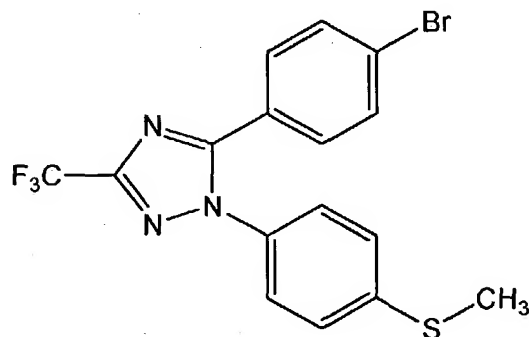
210 mg (yield 65%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 170 mg (0.97 mmol)

of 4-chlorobenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

5 Example 9

5-(4-bromophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 16



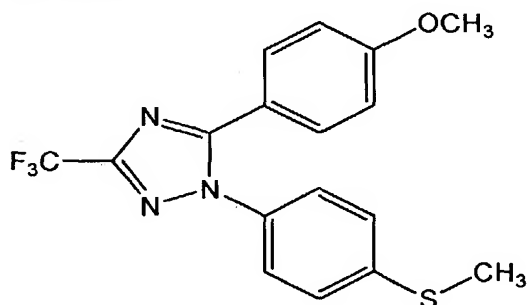
10 280 mg (yield 76%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 213 mg (0.97 mmol) of 4-bromobenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

15

Example 10

1-(4-methylsulfanylphenyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 17



20

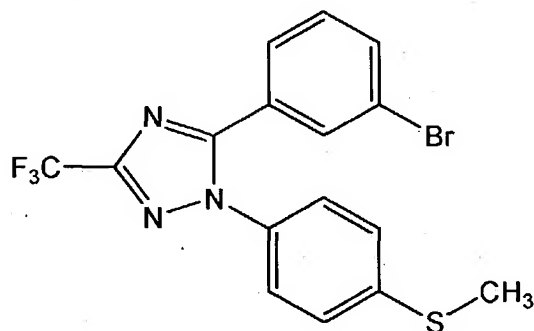
203 mg (yield 69%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 165 mg (0.97 mmol)

of p-anisoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

Example 11

5 5-(3-bromophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H
-[1,2,4]triazole

Formula 18



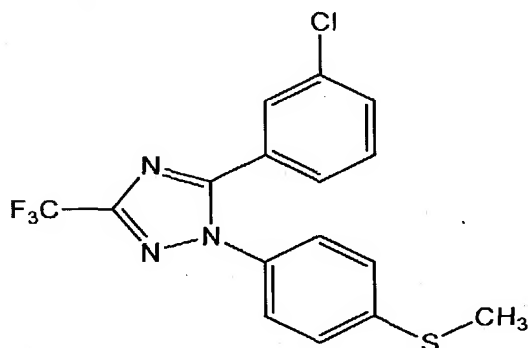
280 mg (yield 76%) of the title compound as an oil was prepared
10 in the same manner as in Example 6 except using 213 mg (0.97 mmol)
of 3-bromobenzoyl chloride instead of p-toluoyl chloride. The title
compound was used in the next step without further purification or
identification.

15

Example 12

5-(3-chlorophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 19



5

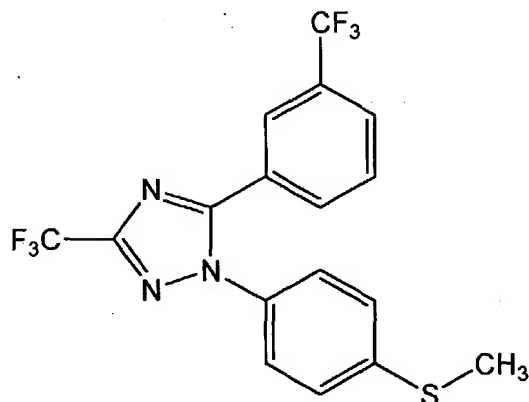
182 mg (yield 72%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 170 mg (0.97 mmol) of 3-chlorobenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or

10

Example 13

5-(3-trifluoromethylphenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 20



15

209 mg (yield 64%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 202 mg (0.97 mmol) of 3-trifluoromethyl benzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or

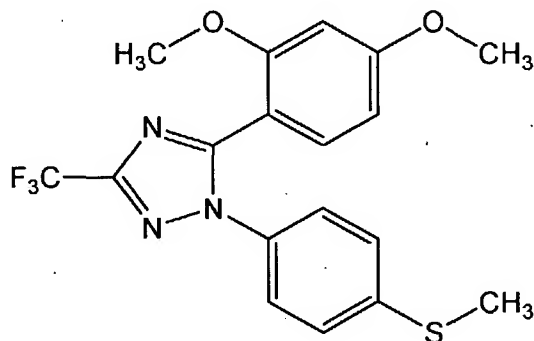
20

identification.

Example 14

5-(2,4-dimethoxyphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 21

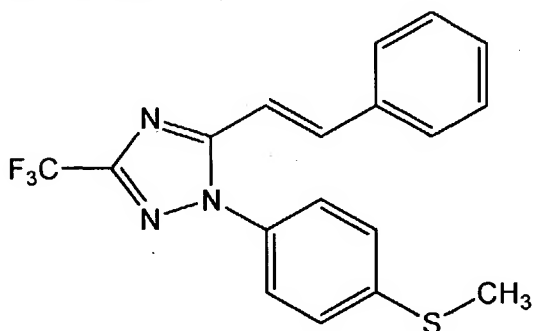


188 mg (yield 54%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 195 mg (0.97 mmol) of 2,4-dimethoxybenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

Example 15

5-styryl-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 22

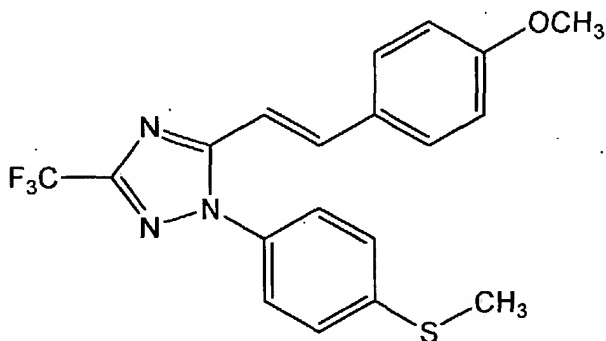


232 mg (yield 73%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 161 mg (0.97 mmol) of cynamoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

Example 16

5-[2-(4-methoxyphenyl)vinyl]-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 23



5

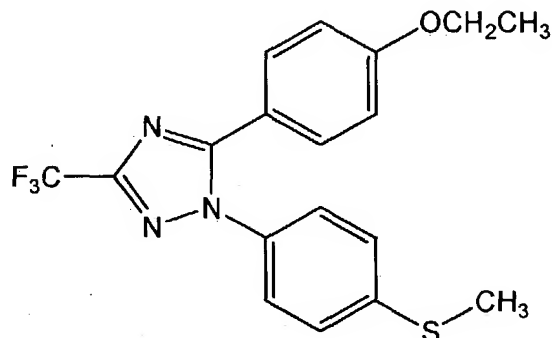
189 mg (yield 55%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 191 mg (0.97 mmol) of 4-methoxycynamoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or

10

Example 17

5-(4-ethoxyphenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 24



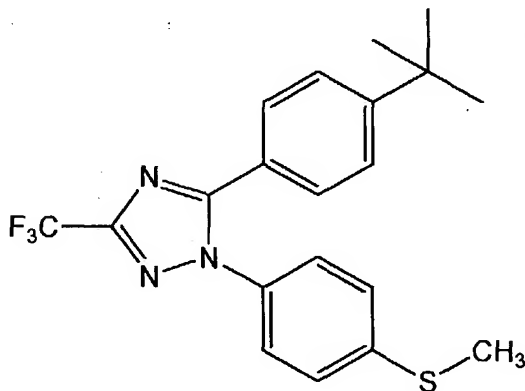
5

243 mg (yield 73%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 181 mg (0.97 mmol) of 4-ethoxybenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or
10 identification.

Example 18

5-(4-t-butylphenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 25



15

282 mg (yield 82%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 193 mg (0.97 mmol) of 4-t-butylbenzoyl chloride instead of p-toluoyl chloride. The title
20 compound was used in the next step without further purification or

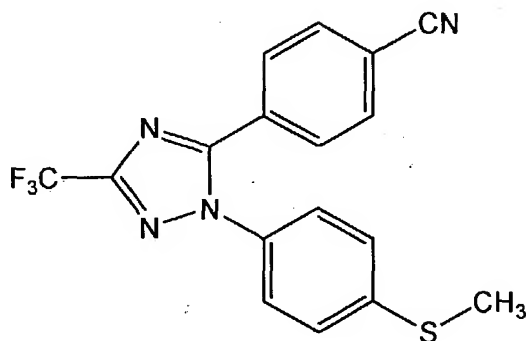
identification.

Example 19

5-(4-cyanophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H

5 -[1,2,4]triazole

Formula 26

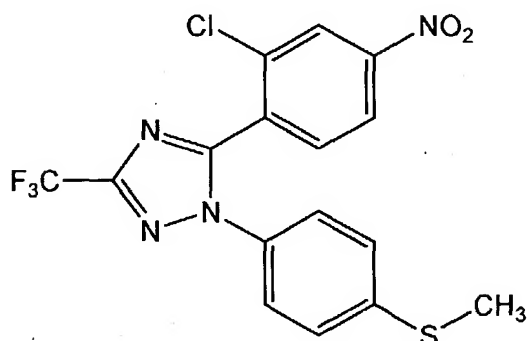


10 165 mg (yield 52%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 163 mg (0.97 mmol) of 4-cyanobenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

Example 20

5-(4-nitro-2-chlorophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 27



5

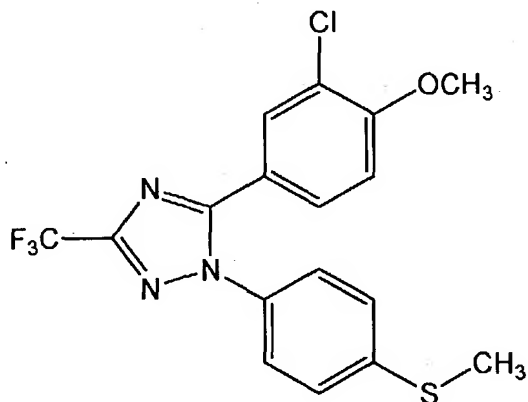
248 mg (yield 68%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 213 mg (0.97 mmol) of 4-nitro-2-chlorobenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or

10

Example 21

5-(3-chloro-4-methoxyphenyl)-1-(4-methylsulfanylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 28



15

215 mg (yield 61%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 200 mg (0.97 mmol) of 3-chloro-4-methoxybenzoyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or

20

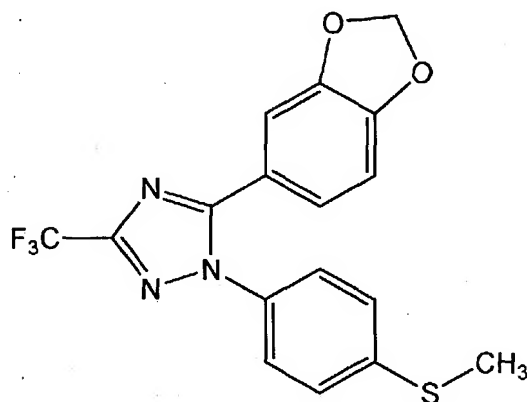
identification.

Example 22

5-benzo[1,3]dioxol-5-yl-1-(4-methylsulfanylphenyl)-3-trifluoromethy

5 1-1H-[1,2,4]triazole

Formula 29

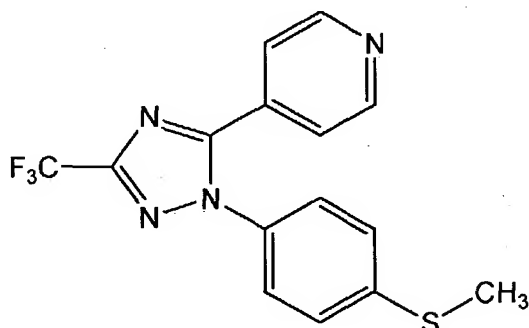


206 mg (yield 59%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 180 mg (0.97 mmol) of benzo[1,3]dioxol-5-yl carbonyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

Example 23

4-[2-(4-methylsulfanylphenyl)-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl]pyridine

Formula 30



5

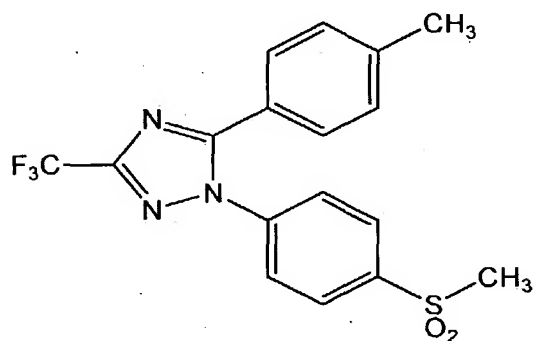
121 mg (yield 41%) of the title compound as an oil was prepared in the same manner as in Example 6 except using 138 mg (0.97 mmol) of isonicotinyl chloride instead of p-toluoyl chloride. The title compound was used in the next step without further purification or identification.

10

Example 24

1-(4-methanesulfonylphenyl)-5-p-tolyl-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 31



15

310 mg (0.89 mmol) of 1-(4-methylsulfanylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole was dissolved in a mixed solvent of dichloromethane (10 ml) and methanol (2 ml) and 710 mg (1.16 mmol) of 80% MMPP was slowly added dropwise. The reaction mixture was stirred at room temperature for 8 hours. When the reaction was completed, the reaction mixture was filtered. The filtrate was washed with sodium bicarbonate and saturated sodium

20

chloride solution (1x each), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 7:3) to give 308 mg (yield 91%) of the title compound as a solid.

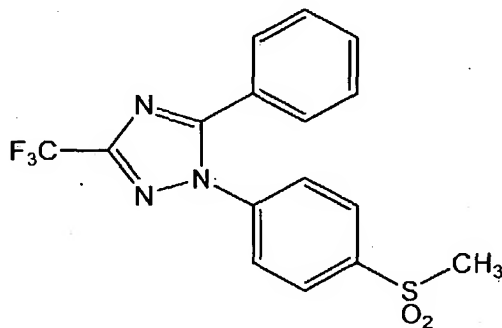
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ 2.45 (s, 3H), 3.15 (s, 3H), 7.23 (d, 2H, $J = 8.2$ Hz), 7.38 (d, 2H, $J = 8.2$ Hz), 7.63 (d, 2H, $J = 8.7$ Hz), 8.03 (d, 2H, $J = 8.7$ Hz).

m.p.: 176 - 178°C.

Example 25

1-(4-methanesulfonylphenyl)-5-phenyl-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 32



283 mg (yield 86%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 300 mg (0.89 mmol) of 1-(4-methylsulfonylphenyl)-5-phenyl-3-trifluoro-1H-[1,2,4]triazole instead of

1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

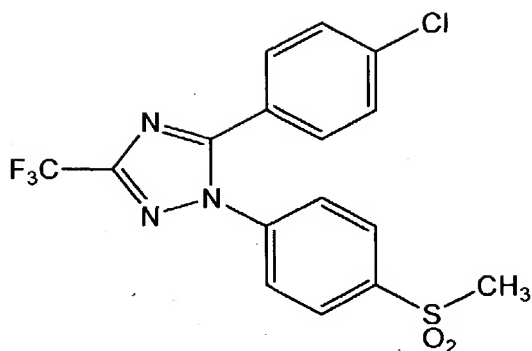
$^1\text{H-NMR}$ (400MHz, CDCl_3): δ 3.15 (s, 3H), 7.42-7.48 (m, 2H), 7.50-7.55 (m, 3H), 7.63 (d, 2H, $J = 8.6$ Hz), 8.03 (d, 2H, $J = 8.6$ Hz).

m.p.: 153-154°C.

Example 26

5-(4-chlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 33



294 mg (yield 82%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 330 mg (0.89 mmol) of

5 5-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

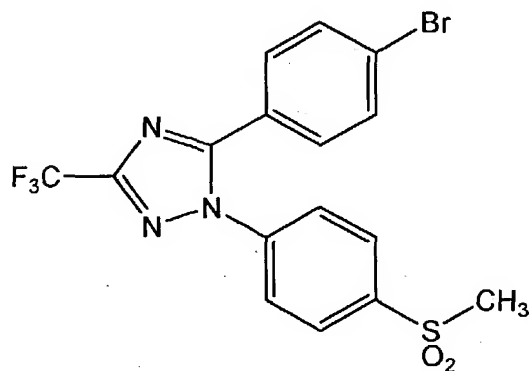
¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.40-7.50 (m, 4H), 7.60 (d, 2H, J = 6.7 Hz), 8.03 (d, 2H, J = 6.7 Hz).

10 m.p.: 190-192°C.

Example 27

5-(4-bromophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-
1H-[1,2,4]triazole

Formula 34



5

365 mg (yield 92%) of the title compound as a solid was prepared
in the same manner as in Example 24 except using 370 mg (0.89 mmol)
of

10 5-(4-bromophenyl)-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazol
e instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.35 (d, 2H, J = 8.5
Hz), 7.50-7.60 (m, 4H), 8.03 (d, 2H, J = 6.3 Hz).

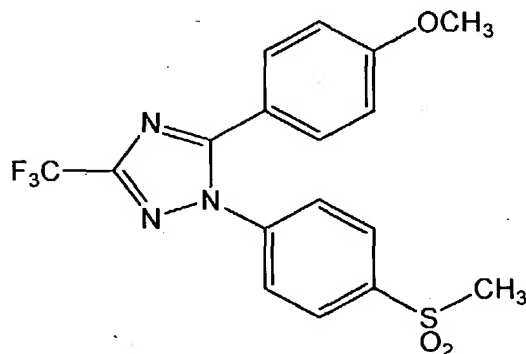
m.p.: 198-199°C.

15

Example 28

1-(4-methanesulfonylphenyl)-5-(4-methoxyphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 35



5

300 mg (yield 85%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 325 mg (0.89 mmol) of

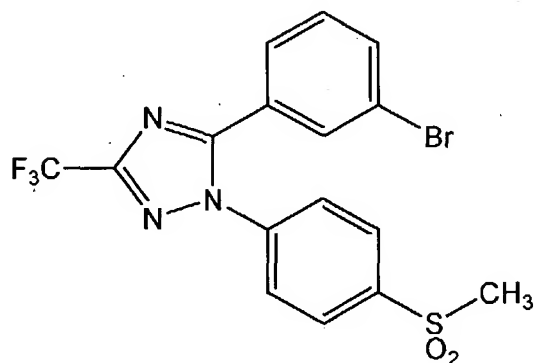
10 1-(4-methylsulfonylphenyl)-5-(4-methoxyphenyl)-3-trifluoro-1H-[1,2,4]triazole instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 3.90 (s, 3H), 6.90 (d, 2H, J = 6.9 Hz), 7.35 (d, 2H, J = 6.9 Hz), 7.65 (d, 2H, J = 8.7 Hz), 8.03 (d, 2H, J = 8.7 Hz).

15 m.p.: 155-156 °C.

Example 29

5-(3-bromophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-
1H-[1,2,4]triazole
Formula 36



5

365 mg (yield 92%) of the title compound as a solid was prepared
in the same manner as in Example 24 except using 370 mg (0.89 mmol)
of

10 e 5-(3-bromophenyl)-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazol instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

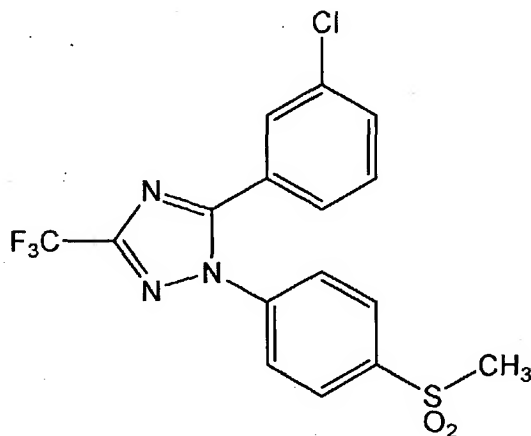
¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.35-7.72 (m, 6H),
7.92 (d, 2H, J = 8.7 Hz).

m.p.: 195-196 °C.

15

Example 30

5-(3-chlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-
1H-[1,2,4]triazole
Formula 37



5

326 mg (yield 91%) of the title compound as a solid was prepared
in the same manner as in Example 24 except using 330 mg (0.89 mmol)
of

10 5-(3-chlorophenyl)-1-(4-methylsulfanylphenyl)-3-trifluoro-1H-[1,2,4]triazol
e instead of
1-(4-methylsulfanylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

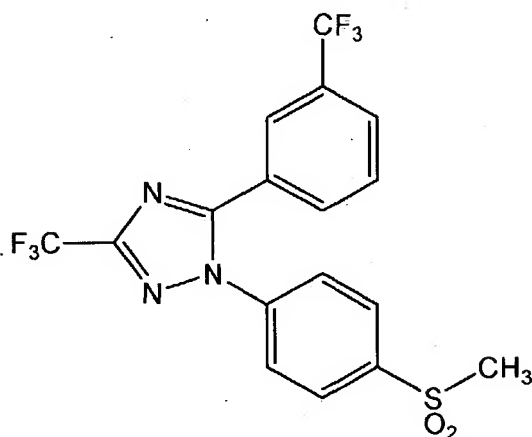
¹H-NMR (400MHz, CDCl₃): δ 3.11 (s, 3H), 7.00 (d, 1H, J = 9.0
Hz), 7.28 (m, 1H), 7.35 (d, 1H, J = 9.0 Hz), 7.62 (s, 1H), 7.64 (d, 2H, J =
9.2 Hz), 8.09 (d, 2H, J = 9.2 Hz).

15 m.p.: 188-190°C.

Example 31

5-(3-trifluoromethylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 38



5

340 mg (yield 88%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 360 mg (0.89 mmol) of

5-(3-trifluoromethylphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.10 (s, 3H), 7.56 (m, 1H), 7.61-7.64 (m, 3H), 7.79 (d, 1H, J = 4.0 Hz), 7.86 (s, 1H), 8.09 (d, 2H, J = 8.8 Hz).

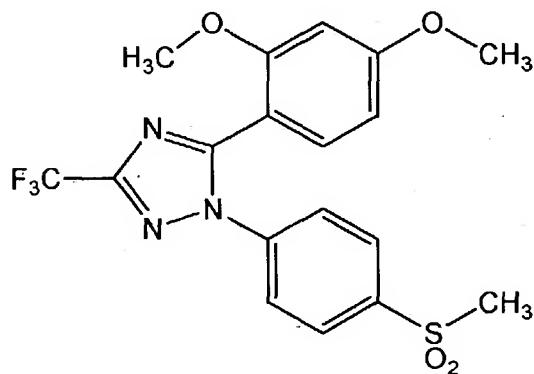
m.p.: 135-137°C.

15

Example 32

5-(2,4-dimethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 39



5

357 mg (yield 94%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 350 mg (0.89 mmol) of

10 5-(2,4-dimethoxyphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

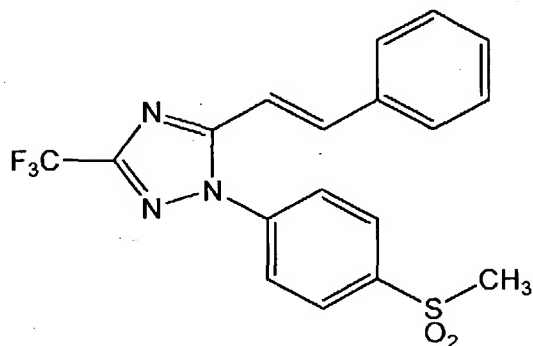
¹H-NMR (400MHz, CDCl₃): δ 3.11 (s, 3H), 3.26 (s, 3H), 3.84 (s, 3H), 6.34 (d, 1H, J = 2.4 Hz), 6.66 (dd, 1H, J = 8.4 Hz, J = 2.4 Hz), 7.58 (d, 1H, J = 8.4 Hz), 7.69 (d, 2H, J = 8.8 Hz), 7.98 (d, 2H, J = 8.8 Hz).

15 m.p.: 110-112°C.

Example 33

5-styryl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 40



5

287 mg (yield 82%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 320 mg (0.89 mmol) of 5-styryl-1-(4-methylsulfonylphenyl)-3-trifluoro-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 6.83 (d, 1H, J = 15.9 Hz), 7.39-7.41 (m, 3H), 7.52-7.54 (m, 2H), 7.82 (d, 2H, J = 8.6 Hz), 8.01 (d, 1H, J = 15.9 Hz), 8.21 (d, 2H, J = 8.6 Hz).

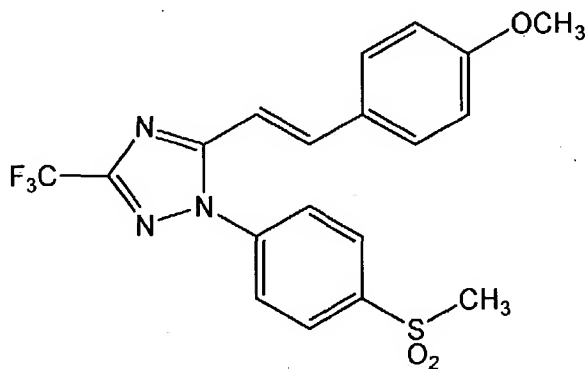
m.p.: 168-170°C.

15

Example 34

5-[2-(4-methoxyphenyl)vinyl]-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 41



5

340 mg (yield 91%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 378 mg (0.89 mmol) of

5-[2-(4-methoxyphenyl)vinyl]-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

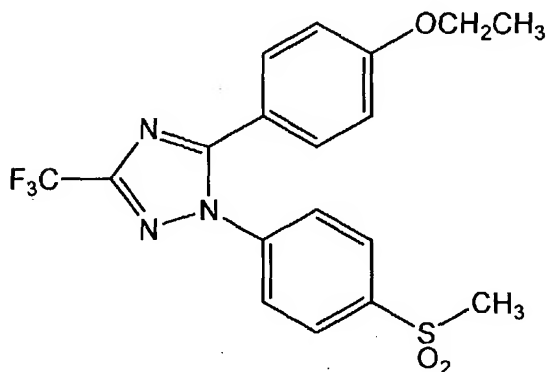
¹H-NMR (400MHz, CDCl₃): δ 3.17 (s, 3H), 3.85 (s, 3H), 6.75 (d, 1H, J = 15.9 Hz), 6.96 (d, 2H, J = 8.7 Hz), 7.50 (d, 2H, J = 8.7 Hz), 7.82 (d, 2H, J = 8.6 Hz), 7.95 (d, 1H, J = 15.9 Hz), 8.21 (d, 2H, J = 8.6 Hz).

15

Example 35

5-(4-ethoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 42



5

300 mg (yield 82%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 337 mg (0.89 mmol) of

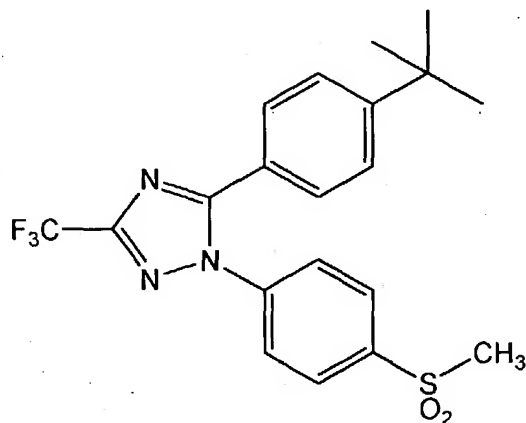
5-(4-ethoxyphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]
10]triazole instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 1.45 (t, 3H, J = 7.0 Hz), 3.15 (s, 3H),
4.10 (q, 2H, J = 7.0 Hz), 6.91 (d, 2H, J = 8.9 Hz), 7.45 (d, 2H, J = 8.9 Hz),
7.65 (d, 2H, J = 8.7 Hz), 8.05 (d, 2H, J = 8.7 Hz).

15 m.p.: 152 – 154 °C.

Example 36

5-(4-t-butylphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-
1H-[1,2,4]triazole
Formula 43



5

343 mg (yield 91%) of the title compound as a solid was prepared
in the same manner as in Example 24 except using 348 mg (0.89 mmol)
of

5-(4-t-butylphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]
10 triazole instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 1.30 (s, 9H), 3.15 (s, 3H), 7.40-7.50
(m, 4H), 7.68 (d, 2H, J = 9.0 Hz), 8.08 (d, 2H, J = 9.0 Hz).

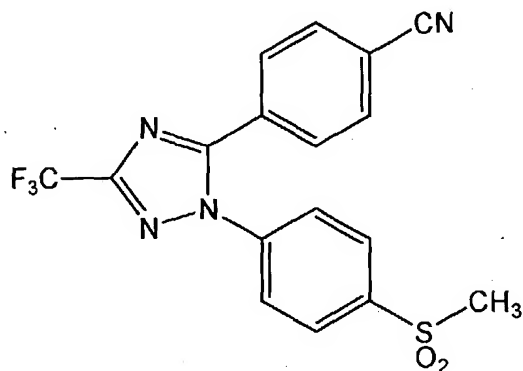
m.p.: 81 – 82°C.

15

Example 37

5-(4-cyanophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 44



5

320 mg (yield 92%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 320 mg (0.89 mmol) of

10 5-(4-cyanophenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4] triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

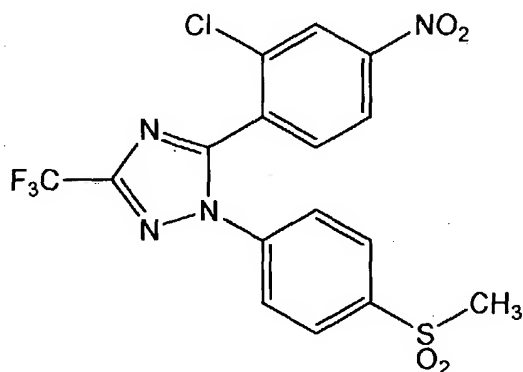
¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.64 (d, 2H, J = 8.8 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.75 (d, 2H, J = 8.7 Hz), 8.13 (d, 2H, J = 8.7 Hz).

15 m.p.: 109 – 111 °C.

Example 38

5-(4-nitro-2-chlorophenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 45



5

314 mg (yield 79%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 369 mg (0.89 mmol) of

5-(4-nitro-2-chlorophenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-
10 -[1,2,4]triazole instead of
1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.51 (d, 2H, J = 8.6 Hz), 7.83 (d, 1H, J = 9.0 Hz), 7.97 (d, 2H, J = 8.6 Hz), 8.29 (d, 1H, J = 9.0 Hz), 8.32 (s, 1H).

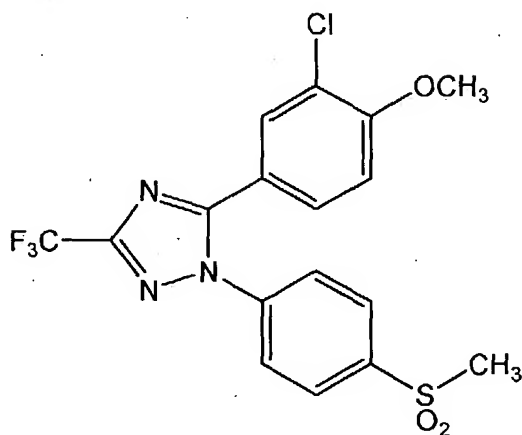
15

m.p.: 110 – 111°C.

Example 39

5-(3-chloro-4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 46



5

319 mg (yield 83%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 356 mg (0.89 mmol) of

5-(3-chloro-4-methoxyphenyl)-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

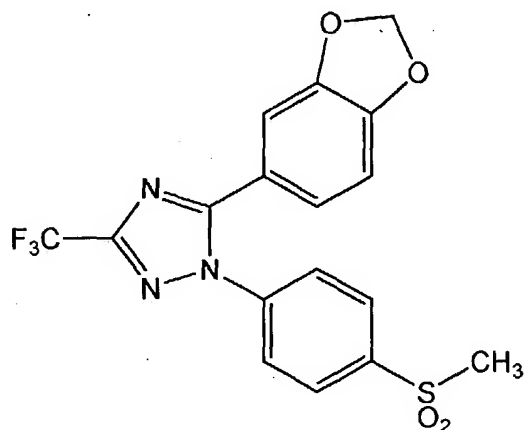
¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 3.95 (s, 3H), 6.90 (d, 1H, J = 8.6 Hz), 7.25 (dd, 1H, J₁ = 8.6 Hz, J₂ = 2.5 Hz), 7.75 (dd, 2H, J₁ = 6.8 Hz, J₂ = 2.0 Hz), 7.76 (d, 1H, J = 2.5 Hz), 8.08 (dd, 2H, J₁ = 8.6 Hz, J₂ = 2.0 Hz).

15

Example 40

5-benzo[1,3]dioxol-5-yl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole

Formula 47



5

322 mg (yield 88%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 337 mg (0.89 mmol) of

5-benzo[1,3]dioxol-5-yl-1-(4-methylsulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

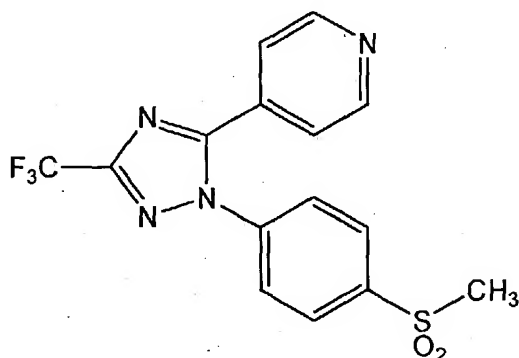
¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 6.05 (s, 2H), 6.82 (d, 1H, J = 7.5 Hz), 6.97-7.02 (m, 2H), 7.65 (d, 2H, J = 8.6 Hz), 8.05 (d, 2H, J = 8.6 Hz).

15

Example 41

4-[2-(4-methanesulfonylphenyl)-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl]pyridine

Formula 48



5

244 mg (yield 72%) of the title compound as a solid was prepared in the same manner as in Example 24 except using 299 mg (0.89 mmol) of

4-[2-(4-methylsulfonylphenyl)-5-trifluoromethyl-2H-[1,2,4]triazol-3-yl]pyridine instead of 1-(4-methylsulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

¹H-NMR (400MHz, CDCl₃): δ 3.15 (s, 3H), 7.45 (d, 2H, J = 6.0 Hz), 7.65 (d, 2H, J = 8.0 Hz), 8.10 (d, 2H, J = 8.0 Hz), 8.75 (d, 2H, J = 6.0 Hz).

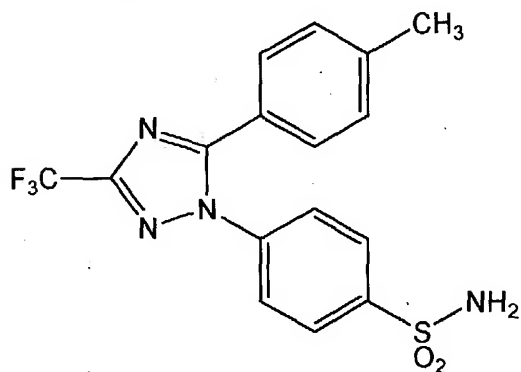
15 m.p.: 180 – 182 °C.

Example 42

4-(5-p-tolyl-3-trifluoromethyl-[1,2,4]triazol-1-yl)benzenesulfonamid

e

Formula 49



5

120 mg (0.32 mmol) of 1-(4-methanesulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole was dissolved in 2 ml of anhydrous tetrahydrofuran and the reaction temperature was adjusted to 0°C. 0.18 ml (0.54 mmol) of 3M solution of methyl magnesium chloride in tetrahydrofuran was added dropwise and the reaction temperature was raised to room temperature. The reaction mixture was stirred at that temperature for 3 hours. 0.9 ml (0.90 mmol) of 1M solution of tributylborane in tetrahydrofuran was added dropwise and refluxed for 18 hours. The reaction temperature was cooled to 0°C. Then, a solution in which 150 mg (1.34 mmol) of hydroxylamine-O-sulfonic acid and 2.56 mg (3.20 mmol) of sodium acetic acid were dissolved in 2 ml of water was slowly added and the reaction mixture was stirred at room temperature for 3 hours. When the reaction was completed, water and ethyl acetate were added and stirred. Then, the resultant solution was three times extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered under reduced pressure, and concentrated under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 7/3) to give 63 mg (yield 52%) of the title compound as a solid.

25

¹H-NMR (400MHz, DMSO-d₆): δ 2.45 (s, 3H), 7.20 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 7.52 (s, 2H), 7.70 (d, 2H, J = 6.6 Hz), 7.98 (d, 2H, J = 6.6 Hz).

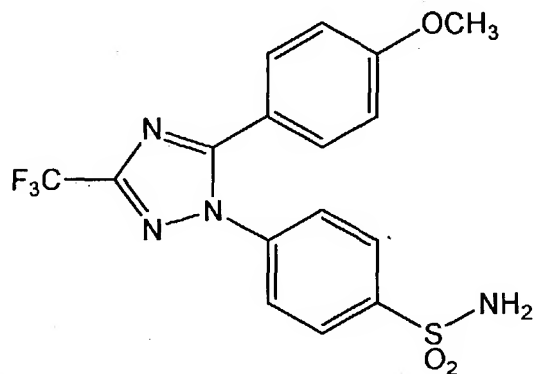
m.p.: 245 – 247 °C.

Example 43

4-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzen

5 e sulfonamide

Formula 50



68 mg (yield 53%) of the title compound as a solid was prepared
in the same manner as in Example 42 except using 127 mg (0.32 mmol)
10 of
1-(4-methylsulfanylphenyl)-5-(4-methoxyphenyl)-3-trifluoro-1H-[1,2,4]triaz
ole instead of
1-(4-methanesulfonylphenyl)-5-p-tolyl-3-trifluoro-1H-[1,2,4]triazole.

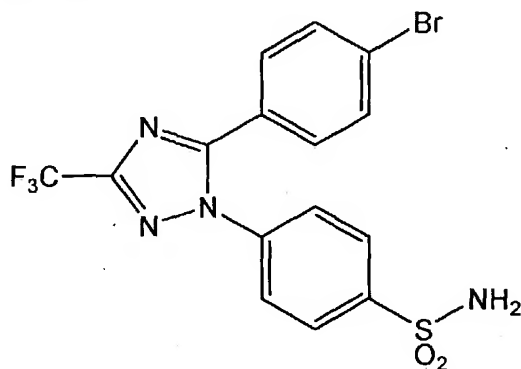
¹H-NMR (400MHz, DMSO-d₆): δ 3.85(s, 3H), 6.96 (d, 2H, J = 6.9
15 Hz), 7.45 (d, 2H, J = 6.9 Hz), 7.55 (s, 2H), 7.75 (d, 2H, J = 8.6 Hz), 7.95
(d, 2H, J = 8.6 Hz).

m.p.: 251 – 253 °C.

Example 44

4-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzene sulfonamide

Formula 51



5

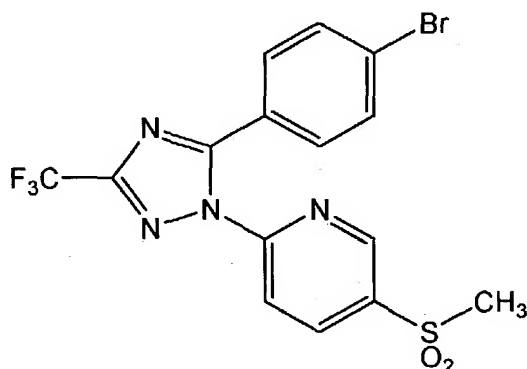
250 mg (0.88 mmol) of N-(4-sulfonamidophenyl)trifluoroacetamidrazone was dissolved in 5 ml of 1,4-dioxane and 0.08 ml (0.97 mmol) of pyridine was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes and 10 212 mg (0.97 mmol) of 4-bromobenzoyl chloride was added dropwise. The reaction mixture was refluxed for 24 hours. When the reaction was completed, the reaction mixture was cooled to room temperature and water and ethyl acetate were added thereto. The water layer was twice 15 extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 1/1) to give 208 mg (yield 53%) of the title compound as an oil.

20 $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 4.95 (br, s, 2H), 7.39 (d, 2H, $J = 8.7$ Hz), 7.58-7.62 (m, 4H), 8.05 (d, 2H, $J = 8.7$ Hz).

Example 45

2-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine

Formula 52



5

130 mg (0.46 mmol) of N-(5-methanesulfonylpyridin-2-yl)trifluoroacetamidrazone was dissolved in 5 ml of 1,4-dioxane and 0.04 ml (0.51 mmol) of pyridine was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes and 115 mg (0.51 mmol) of 4-bromobenzoyl chloride was added dropwise. The reaction mixture was stirred at 110°C under reflux for 24 hours. When the reaction was completed, the reaction mixture was cooled to room temperature and water and ethyl acetate were added thereto. The water layer was twice extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 3:7) to give 107 mg (yield 52%) of the title compound as a solid.

20 ¹H-NMR (400MHz, CDCl₃): δ 3.42 (s, 3H), 7.55 (d, 2H, J = 6.7 Hz), 7.70 (d, 2H, J = 6.7 Hz), 8.15 (d, 1H, J = 8.5 Hz), 8.65 (dd, 1H, J₁ = 8.5 Hz, J₂ = 2.1 Hz), 8.95 (d, 1H, J = 2.1 Hz).

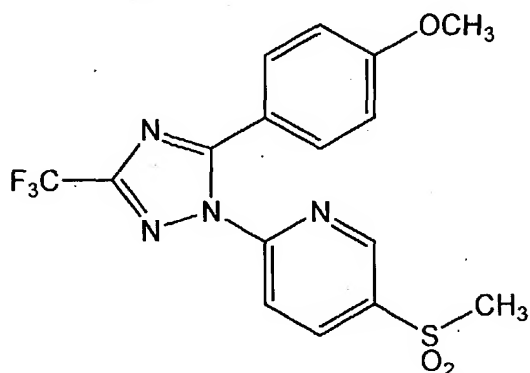
m.p.: 143-145°C.

25

Example 46

2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1.2.4]triazol-1-yl]-5-methanesulfonyl pyridine

Formula 53



5

108 mg (yield 59%) of the title compound as a solid was prepared in the same manner as in Example 45 except using 87 mg (0.51 mmol) of p-anisoyl chloride instead of 4-bromobenzoyl chloride.

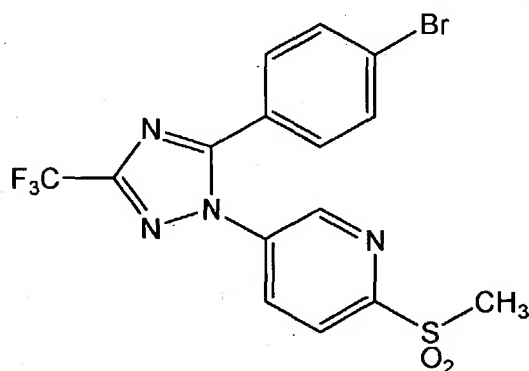
¹H-NMR (400MHz, CDCl₃): δ 3.25(s, 3H), 3.85 (s, 3H), 6.90 (d, 2H, J = 6.8 Hz), 7.50 (d, 2H, J = 6.7 Hz), 7.95 (d, 1H, J = 8.5 Hz), 8.45 (dd, 1H, J₁ = 8.5 Hz, J₂ = 2.1 Hz), 8.95 (d, 1H, J = 2.1 Hz).

m.p.: 138 – 139 °C.

Example 47

2-methanesulfonyl-5-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]pyridine

Formula 54



130 mg (0.46 mmol) of N-(2-methanesulfonylpyridin-5-yl)trifluoroacetamidrazone was dissolved

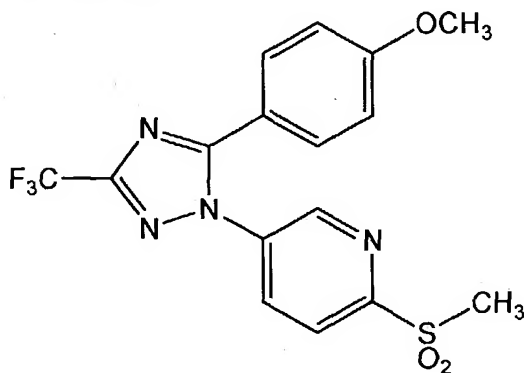
in 5 ml of 1,4-dioxane and 0.04 ml (0.51 mmol) of pyridine was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes and 115 mg (0.51 mmol) of 4-bromobenzoyl chloride was added dropwise. The reaction mixture was stirred at 110°C under reflux for 24 hours. When the reaction was completed, the reaction mixture was cooled to room temperature and water and ethyl acetate were added thereto. The water layer was twice extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 3:7) to give 107 mg (yield 52%) of the title compound as a solid.

¹H-NMR (400MHz, CDCl₃): δ 3.42 (s, 3H), 7.55 (d, 2H, J = 6.7 Hz), 7.70 (d, 2H, J = 6.7 Hz), 8.22 (d, 1H, J = 8.5 Hz), 8.55 (dd, 1H, J₁ = 8.5 Hz, J₂ = 2.1 Hz), 8.95 (d, 1H, J = 2.1 Hz).

m.p.: 141-143°C.

Example 48

2-methanesulfonyl-5-[5-(4-methoxyphenyl)-3-trifluoromethyl-1,2,4-triazol-1-yl]pyridine
Formula 55



108 mg (yield 59%) of the title compound as a solid was prepared in the same manner as in Example 47 except using 87 mg (0.51 mmol) of p-anisoyl chloride instead of 4-bromobenzoyl chloride.

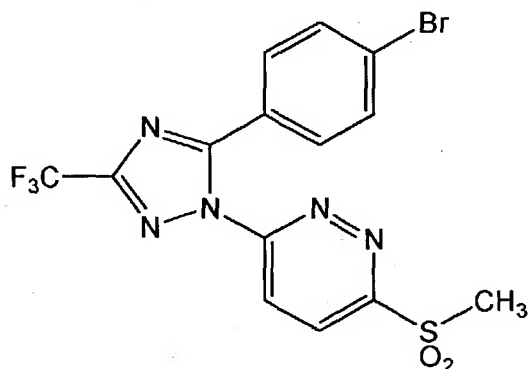
¹H-NMR (400MHz, CDCl₃): δ 3.25(s, 3H), 3.85 (s, 3H), 6.90 (d, 2H, J = 6.8 Hz), 7.50 (d, 2H, J = 6.7 Hz), 7.85 (d, 1H, J = 8.5 Hz), 8.35 (dd, 1H, J₁ = 8.5 Hz, J₂ = 2.1 Hz), 8.90 (d, 1H, J = 2.1 Hz).

m.p.: 136 – 137°C.

Example 49

3-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine

Formula 56



5

310 mg (1.09 mmol) of N-(6-methanesulfonylpyridazin-3-yl)trifluoroacetamidrazone was dissolved in 10 ml of 1,4-dioxane and 0.10 ml (1.20 mmol) of pyridine was added dropwise. The reaction mixture was stirred at room temperature for 10 minutes and 264 mg (1.20 mmol) of 4-bromobenzoyl chloride was added dropwise. The reaction mixture was stirred at 110°C under reflux for 24 hours. When the reaction was completed, the reaction mixture was cooled to room temperature and water and ethyl acetate were added thereto. The water layer was twice extracted with ethyl acetate. The combined organic layer was once washed with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered under reduced pressure. The obtained crude product was purified by flash column chromatography (ethyl acetate/n-hexane = 3:7) to give 220 mg (yield 45%) of the title compound as a solid.

20

¹H-NMR (400MHz, CDCl₃): δ 3.42 (s, 3H), 7.55 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz), 8.38 (d, 1H, J = 9.0 Hz), 8.45 (d, 1H, J = 9.0 Hz).

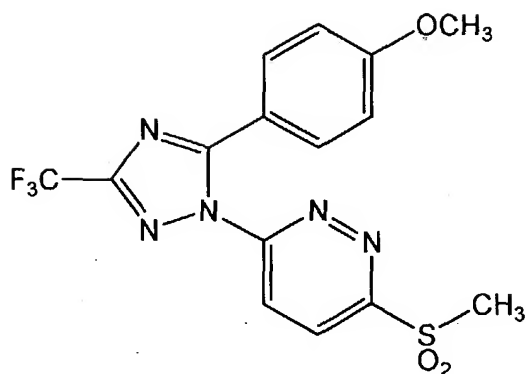
m.p.: 174-181°C.

25

Example 50

3-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-6-methanesulfonyl pyridazine

Formula 57



183 mg (yield 42%) of the title compound as a solid was prepared in the same manner as in Example 49 except using 205 mg (0.51 mmol) of p-anisoyl chloride instead of 4-bromobenzoyl chloride.

¹H-NMR (400MHz, CDCl₃): δ 3.42(s, 3H), 3.85 (s, 3H), 6.85 (d, 2H, J = 6.8 Hz), 7.55 (d, 2H, J = 6.8 Hz), 8.20 (d, 1H, J = 9.1 Hz), 8.35 (d, 1H, J = 9.1 Hz).

m.p.: 185 – 186 °C.

Experiments

1. Evaluation of selective COX-2 inhibitory activity

1) Method

In order to pharmacologically determine the selective COX-2 inhibitory activity, the percentages of the COX-1 and COX-2 inhibition of the compounds of the present invention illustrated in the Examples were measured by the following methods.

a. Assay for the COX-1 inhibitory activity using U-937

U-937 human lymphoma cells (Korean Cell Line Bank, Seoul, Korea, Accession Number: 21593) were cultured and centrifuged. The collected cells were diluted with HBSS (x1, Hank's balanced salt solution) to a concentration of 1 x 10⁶ cells/ml. 1 ml of the dilute cell solution was placed into each well of 12-well plates. 5 μl of 1 μM solution of a test compound in DMSO and 5 μl of DMSO as a control were added to the wells. The wells were incubated in CO₂ incubator at 37 °C for 15 minutes. Separately, 10 mM stock solution of arachidonic acid in ethanol was diluted ten times in ethanol to prepare 1 mM solution of arachidonic acid. Arachidonic acid acts as a substrate. 10 μl of

the 1 mM solution of arachidonic acid was added to each well and incubated at CO₂ incubator at 37°C for 30 minutes. The cell solution of each well was placed in a centrifuge test tube and centrifuged at 10,000 rpm at 4°C for 5 minutes. The concentration of PGE2 in the collected
 5 cells and the supernatant was quantified by means of a monoclonal kit (Cayman Chemicals). The percentages of PGE2 inhibition in a group of the test compound-treated cells in relation to a group of the DMSO-treated cells were calculated. Based on the calculated values, the COX-1 inhibitory activities were evaluated.

10 b. Assay for the COX-2 inhibitory activity using RAW 264.7 cell line

2 x 10⁶ cells of RAW 264.7 cell line (Korean Cell Line Bank, Seoul, Korea, Accession Number: 40071) were inoculated into each well
 15 of 12-well plates. Each well was treated with 250 μ M of aspirin and incubated at 37°C for 2 hours. After the culture media were replaced with new culture media, the new culture media were treated with a test compound (10 nM) and incubated for 30 minutes. Then, each well was treated with interferon γ (100 units/ml) and lipopolysaccharide (LPS, 100
 20 ng/ml) and incubated for 18 hours. The culture media were transferred to another test tubes. The concentration of PGE2 was quantified by means of the EIA kit (Cayman Chemicals).

25 2) Test results

The test results are presented in Table 1 below. The percentages of the COX inhibition were calculated according to the following equation:

$$\% \text{ Inhibition} = (\text{concentration of PGE2 in test compound-untreated sample} - \text{concentration of PGE2 in test compound-treated sample}) / (\text{concentration of PGE2 in test compound-untreated sample}) \times 100$$

Table 1
Cyclooxygenase (COX) Inhibition (%)

Samples	COX-1 (1 μ M)	COX-2 (10 nM)
Reference (Valdecoxib)	28.8	5.47
Example 25	29.2	7.62
Example 26	38.8	10.53
Example 27	13.8	16.04

Example 28	10.1	28.62
Example 29	16.7	6.23
Example 30	18.6	7.32
Example 31	16.5	5.66
Example 32	19.9	12.6
Example 33	19.2	19.23
Example 34	23.5	26.82
Example 35	11.8	38.65
Example 36	21.6	6.23
Example 37	23.7	8.92
Example 38	19.5	5.95
Example 39	12.5	32.62
Example 40	18.7	33.73
Example 41	16.7	8.88
Example 42	38.0	12.08
Example 43	34.6	32.32
Example 44	23.1	29.86
Example 45	14.6	33.63
Example 46	12.6	42.32
Example 47	21.9	4.26
Example 48	28.8	5.63
Example 49	14.6	3.21
Example 50	10.6	4.32

3) Evaluation

The *in vitro* test results about the percentages of the COX-1 and COX-2 inhibition are listed in Table 1.

As shown in Table 1, inhibition (%) ratios of COX-2 to COX-1 in
5 Examples 24 and 50 were equal to or higher than that in the reference, Valdecoxib. This indicates that selective inhibition of COX-2 to COX-1 of the present compound is the same as or superior to that of the reference. In particular, in the case of
10 1-(4-methanesulfonylphenyl)-5-(4-methoxyphenyl)-3-trifluoro-1H-[1,2,4]triazole of Example 28,
1-(4-methanesulfonylphenyl)-5-(4-ethoxyphenyl)-3-trifluoro-1H-[1,2,4]triazole of Example 35,
5-(3-chloro-4-methoxyphenyl)-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole of Example 39,
15 5-bezo[1,3]dioxol-5-yl-1-(4-methanesulfonylphenyl)-3-trifluoromethyl-1H-[1,2,4]triazole of Example 40,
4-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzene sulfonamide of Example 44,
2-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfo

nyl pyridine of Example 45, and 2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine of Example 46, the COX-2 inhibitory activities were remarkably enhanced in comparison with the reference. At the same time, the COX-1 inhibitory activities were the same as or lower than that of the reference. Therefore, it can be said that these compounds have excellent selectivities.

All the compounds of Examples except Examples 47, 49, and 50 exhibited the COX-2 inhibitory activities higher than the reference. Based on this result, it can be seen that the present compounds have reduced side effects due to enhanced selectivity and improved relief effects of fever, pain, and inflammation, compared to the reference.

2. Carrageenan-induced paw edema test in rats

1) Method

The day before the test date, rats were selected in each group so that the average body weight was as close as possible, and the rats were fasted by feed withdrawal prior to the test. At the test date, the rats were orally administered with the test compounds and a control material.

After 1 hour, the volume (V_{0h}) of a predetermined portion of the left hind foot of the rats was measured with a plethysmometer. 100 μ l of 1% carrageenan solution was subcutaneously injected to the left hind foot of the rats using a syringe with 1 ml capacity. Three hours after the injection of the carrageenan, the volume (V_{3h}) of the predetermined portion of the foot was again measured. The foot swelling variation ($T_{3h} - T_{0h}$) in a group of test compound-treated rats was compared with that of a group of control material-treated rats. With the supposition of 0% inhibition by the control (control material-treated rats), the inhibition percentage of edema of each test compound was determined.

2) Test results

The test results are presented in Table 2 below.

Table 2

Cyclooxygenase (COX) inhibitory effect (% inhibition)

Samples	Inhibitory effect (% inhibition)
Reference 1 (Indomethacine)	40.1

Reference 2 (Celecoxib)	23.9
Example 27	21.7
Example 28	23.3
Example 34	19.3
Example 35	32.3
Example 43	39.1
Example 44	28.8
Example 45	21.6
Example 46	33.4

3) Evaluation

The *in vivo* test results of the percentage of COX inhibition are listed in Table 2.

5 As shown in Table 2, the % inhibition of the compounds in Examples 27 to 46 against COX was almost the same as or much higher than that of the Celecoxib. This indicates that the compounds of the present invention have almost the same or higher COX inhibitory effects, compared to the Celecoxib. In particular, in the case of
10 1-(4-methanesulfonylphenyl)-5-(4-ethoxyphenyl)-3-trifluoro-1H-[1,2,4]triazole of Example 35, 4-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide of Example 43, 4-[5-(4-bromophenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]benzenesulfonamide of Example 44, and
15 2-[5-(4-methoxyphenyl)-3-trifluoromethyl-[1,2,4]triazol-1-yl]-5-methanesulfonyl pyridine of Example 46, the COX inhibitory effects were remarkably improved in comparison with the Celecoxib.

In addition, all the compounds of Examples except Example 34
20 exhibited the same or higher COX inhibitory effects in comparison with the Celecoxib. Therefore, it can be seen that the compounds of the present invention have improved relief effects of fever, pain, and inflammation.

As apparent from the above description, the present invention
25 provides a 1,2,4-triazole derivative or a non-toxic salt thereof, a preparation method thereof, and a pharmaceutical composition containing the derivative or the salt as an active ingredient. The pharmaceutical composition is effective in reducing fever, pain, and inflammation. In particular, as a result of reduction of the side effects of

conventional nonsteroidal antiinflammatory agents, the pharmaceutical composition is useful for treating patients with peptic ulcer disease, gastritis, regional enteritis, ulcerative colitis, diverticulitis, gastrorrhagia, or hypoprothrombinemia.

5 While the present invention has been particularly shown and described with reference to exemplary embodiments thereof, it will be understood by those of ordinary skill in the art that various changes in form and details may be made therein without departing from the spirit and scope of the present invention as defined by the following claims.

10